DOCUMENT RESUME

ED 478 365 CG 032 473

TITLE	A Collection of NIDA Notes: Articles That Address Research on Club Drugs.
INSTITUTION	National Inst. on Drug Abuse (DHHS/PHS), Bethesda, MD.
REPORT NO	NN0060
PUB DATE	2003-07-00
NOTE	68p.
AVAILABLE FROM	For full text: http://165.112.78.61/NIDA_Notes/ NN0060.html.
PUB TYPE	Collected Works - General (020)
EDRS PRICE	EDRS Price MF01/PC03 Plus Postage.
DESCRIPTORS	Drug Abuse; *Illegal Drug Use; *Research
IDENTIFIERS	*Ecstasy (Drug); *Methamphetamines

ABSTRACT

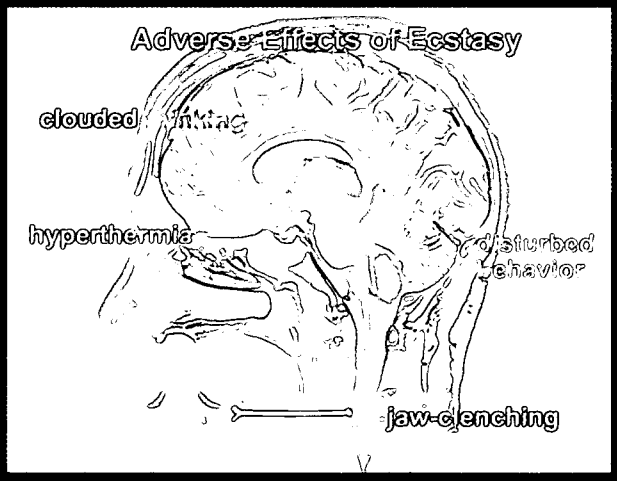
Included in this document are selections of topic-specific articles on club drug research reprinted from the National Institute on Drug Abuse's (NIDA) research newsletter, NIDA Notes. The collection features articles originally published from 1996 through 2002. Topics include the effects of ecstasy and methamphetamine on the brain and body, prenatal exposure to ecstasy, research aimed at reversing methamphetamine's neurotoxic effects, the epidemiology of club drug use, NIDA's initiatives to control the use of club drugs, and LDS, PCP, GHB, and ketamine. (GCP)

A Collection of

NIDA NOTES

NATIONAL INSTITUTE ON DRUG ABUSE

Articles That Address



RESEARCH ON CLUB DRUGS

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse

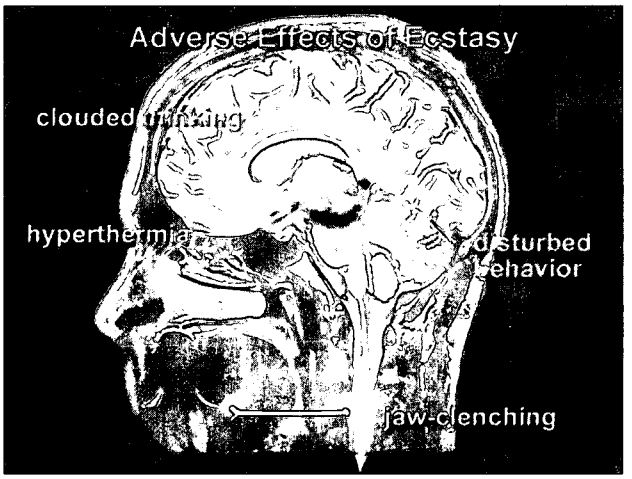
NN0060

A Collection of

NIDA NOTES

NATIONAL INSTITUTE ON DRUG ABUSE

Articles That Address



RESEARCH ON CLUB DRUGS

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse

Introduction

The National Institute on Drug Abuse (NIDA) supports more than 85 percent of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, including addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and evaluation of effective messages to deter young people, in particular, from abusing drugs.

Included in this document are selections of topic-specific articles reprinted from NIDA's research newsletter, *NIDA NOTES.* Six times per year, *NIDA NOTES* reports on important highlights from NIDA-sponsored research, in a format that specialists and lay readers alike can read and put to use. Selections like the current one are intended to remind regular *NIDA NOTES* readers and inform other readers of important research discoveries during the periods they cover.

We hope the information contained here answers your needs and interests. To subscribe to *NIDA NOTES* and for further information on NIDA's drug abuse and addiction research, please visit our Web site at www.drugabuse.gov.

Table of Contents

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 17, Number 3 (October 2002)

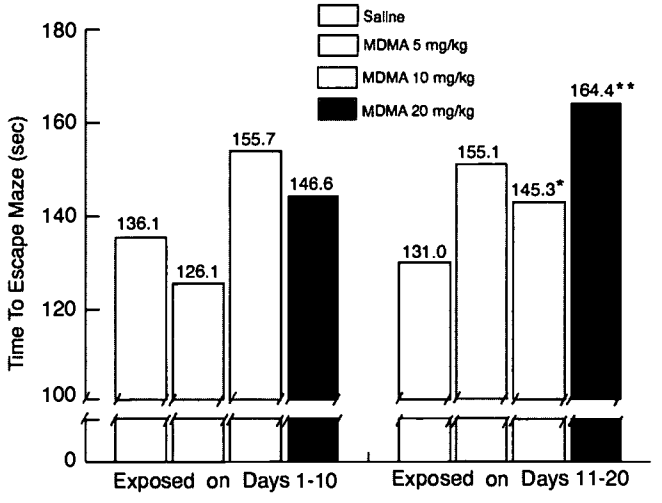
Prenatal Exposure to Ecstasy May Impair Memory and Cognition

By Jill S. Williams, *NIDA NOTES* Contributing Writer

Dr. Harry Broening, Dr. Charles Vorhees, and colleagues at the Cincinnati Children's Research Foundation and the University of Cincinnati have demonstrated that rats exposed to MDMA—ecstasy—during the developmental period corresponding to the third trimester of human pregnancy suffer memory and learning deficiencies that persist into adulthood.

Scientific studies have already established that ecstasy users are at risk for dehydration, hypertension, hyperthermia, and heart or kidney failure. The drug also has been shown to damage nerves in the brain's serotonin system and appears to produce long-term deficits in memory and cognition. The new study suggests that unborn children of ecstasy users may suffer deleterious effects that last into adulthood. "The possibility that these findings in rats may also apply to humans raises a concern because this drug, which is incorrectly perceived as safe by many of its proponents, is sometimes being used by young women who are pregnant," says Dr. Jerry Frankenheim of NIDA's Division of Neuroscience and Behavioral Research.

Animals Exposed to MDMA Take Longer To Escape Multiple-T Water Maze



*p<0.05, **p<0.01

Adult rats that had been exposed to MDMA doses of 10 or 20 mg/kg body weight (comparable to doses used by human MDMA abusers) on days 11 to 20 after birth (a period comparable to late in the third trimester of human pregnancy) took significantly longer to escape the multiple-T water maze than did animals exposed to saline solution. No statistically significant increase in escape times was observed among rats exposed on days 1 to 10 after birth.

Timing and Vulnerability

In designing the current study, the researchers drew on previous studies by Dr. Vorhees on the effects of methamphetamine exposure on rodent brain development. These studies identified specific periods late in rodent brain development—days 11 to 20 after birth, which are analogous to late third-trimester human fetal brain development—in which the brain is quite vulnerable to methamphetamine-induced impairments of spatial learning and memory. The question became, can related drugs, such as MDMA and other synthetic stimulants, also cause such impairments?

Dr. Vorhees and his colleagues decided to test the effects of MDMA administered to rats at this same crucial 11 to 20 days postnatal developmental period and to a comparison group of rats on days 1 to 10 after birth (comparable to early third trimester of human pregnancy). According to Dr. Vorhees, the dosages given to rats in the study are equivalent to a 110-lb woman taking 25 mg, a common dose for MDMA users, up to 250 mg, an amount sometimes reached or exceeded by chronic abusers.

Testing for Learning, Memory

When the rats reached young adulthood, the researchers put them through a series of maze and swimming trials to assess the effects of MDMA exposure on learning and memory. An initial test revealed no significant differences between the MDMA-exposed rats and the controls in terms of swimming performance or motivation to escape from the water. Next, animals were evaluated in a test of sequential learning called the multiple-T (Cincinnati) water maze. The rats had to search through nine decision points to find their way through the maze and out of the water. The researchers found that the rats exposed to MDMA on days 11 to 20 after birth made significantly more errors and took significantly longer to escape the maze than did either the MDMA-unexposed animals or those exposed to MDMA on days 1 to 10 after birth.

"The animals exposed to MDMA during the critical 11 to 20 days postnatal brain development period cannot seem to eliminate errors the way normal animals do," says Dr.

Vorhees. "The difference is the rate at which they learn. All of the animals eventually learned how to navigate the maze, but it took the MDMA-exposed animals significantly longer to do so."

The Morris hidden platform maze was used to further evaluate the animals' spatial memory and cognitive abilities. A 6-foot diameter swimming pool was constructed and a small clear acrylic platform was placed so that the animals could escape if they found it. In increasingly difficult phases the rats had to find the platform when it was above the water, below the water, moved to a new location, or below the water and reduced in size. Memory trials were also performed with the platform removed. Animals exposed to MDMA on days 1 to 10 after birth performed as well as unexposed animals on the trials. However, the animals exposed to MDMA on days 11 to 20 after birth showed significant impairment of memory and spatial learning when the platform was submerged and on memory trials when the platform was removed, but no differences when the platform was above the water.

"These later trials test the animals' ability to remember something in space," explains Dr. Vorhees. "We found that as we made the task harder, MDMA-exposed animals had a disproportionately harder time finding the platform. The harder the task was, the more their learning disability was revealed."

Comparing Infant Versus Adult Exposure

Upon completion of the trials, the rats were sacrificed and their brains were preserved for later analysis. The researchers wanted to know if animals exposed to MDMA during early brain development would show the same pattern of damage to neurotransmitters that has been shown in adult animals exposed to MDMA. They did not.

"This was a surprise because we didn't find the same damage to neurotransmitters as was found in previous studies of animals exposed to MDMA as adults," says Dr. Vorhees. "Yet, the animals in the current study still show cognitive impairment, as demonstrated by their performance on the learning and memory trials." He hypothesizes that a different mechanism is at work in animals exposed to MDMA during brain development that later affects their memory and learning ability. Future research will focus on identifying this mechanism.

Dr. Frankenheim points out that this research is a warning that what is happening in animals may also happen with people. "The work of determining what drugs of abuse do to fetuses when the mother takes them is very difficult. It is not yet known whether human fetuses exposed to MDMA will develop persistent memory and learning problems. However, these findings in rats raise the concern that MDMA may pose a previously unrecognized risk to the developing human brain," he says.

Future research will involve determining the effects of MDMA exposure at earlier points in fetal development, such as during the period corresponding to the first trimester in humans, when drug exposure is more likely for women who may not yet be aware that they are pregnant. The first trimester is also the developmental period when humans are most sensitive to neurotoxins.

Source

- Broening, H.W.; Morford, L.L.; Inman-Wood, S.L.; Fukumura, M.; and Vorhees, C.V. 3,4-methylenedioxymethamphetamine (ecstasy)-induced learning and memory impairments depend on the age of exposure during early development. *Journal of Neuroscience* 21(9):3228-3235, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 2 (May 2002)

New Teaching Aids Focus on Ecstasy (MDMA), Power of Science

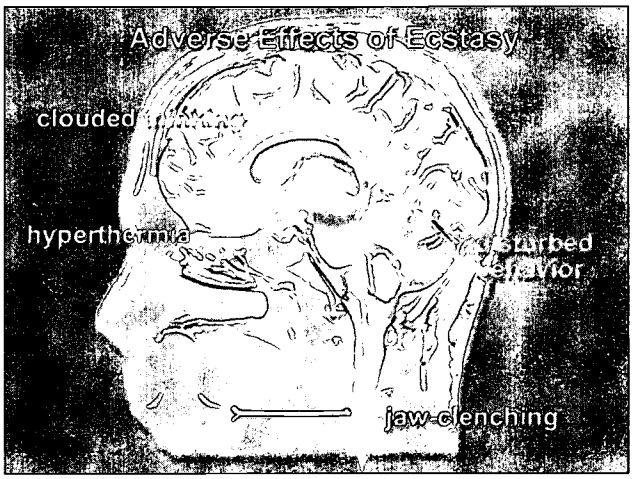
NIDA has added a presentation that focuses on the risks of the club drug ecstasy (MDMA) and a presentation describing NIDA's science-based investigation of the causes and effects of drug abuse to its series of slide teaching packets, which are designed for use by health practitioners, teachers, and neuroscientists.

"The Neurobiology of Ecstasy (MDMA)," packet IV in the series, contains 20 color slides, an accompanying script, and guidance for creating a slide presentation. It describes MDMA's effects on the brain's serotonin pathway and the drug's short- and long-term adverse effects. The packet also includes a list of additional teaching resources and links to related Web pages, such as *NIDA NOTES* articles on ecstasy and NIDA's Web site on club drugs, www.clubdrugs.org.

Packet V incorporates NIDA's mission in its title, "Bringing the Power of Science To Bear on Drug Abuse and Addiction." The materials in this packet, which was designed primarily for use in middle schools, include 14 color slides illustrating how NIDA-supported research has led to an understanding of the effects of drugs and has been used to develop treatment and prevention programs. The packet also introduces the audience to NIDA's Web site as a resource for accurate drug abuse information.

All of the slide teaching packets include text that instructors can incorporate into a 30- to 40-minute presentation. The text can be used as a narrative "script" or can be customized for different audiences. The slide teaching packets are available for download from the Web site at www.drugabuse.gov/Teaching.html. This NIDA site also includes guidance for creating slides from the downloaded files. A new CD containing the first four slide packets is available as publication #AVD145 from the National Clearinghouse for Alcohol and Drug Information at 800-729-6686 (800-487-4889 for the deaf). In addition to the ecstasy teaching packet, "The Brain and the Actions of Cocaine, Opiates, and Marijuana," "The Neurobiology of Drug Addiction," and "Understanding Drug Abuse and Addiction: What Science Says" are included in the CD. NN

Examples of Slides and Narrative Text in NIDA's New Teaching Packets



"People who take ecstasy desire its pleasurable or reinforcing effects. However, few drugs are able to produce desirable effects without also producing side effects. Ecstasy is no exception, and there are several side effects or adverse effects that can occur, especially if the dose increases. Some people who take only one ecstasy pill may have negative psychological effects such as clouded thinking, agitation and disturbed behavior."

"Forget the stereotype of a drug addict hanging out on a dangerous street corner. Anyone can get hooked on drugs — your friends, members of your family, your neighbors. Trying a drug just because a friend says it's 'cool,' might cost you much more than you bargained for.... Is it worth the risk?"

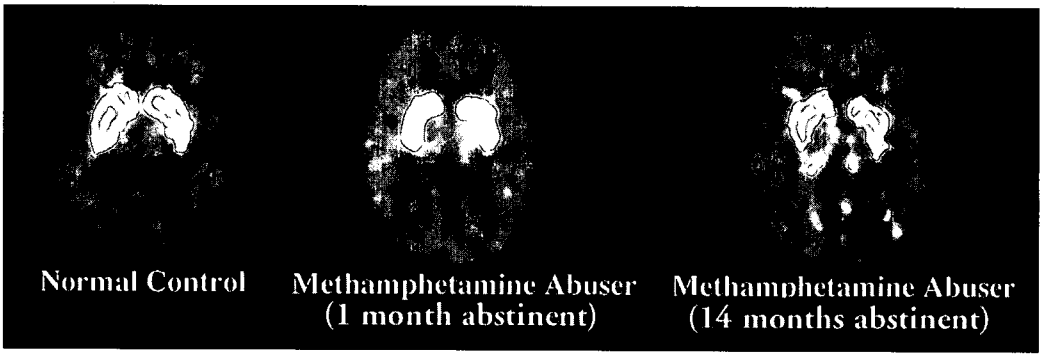
NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 1 (April 2002)

Methamphetamine Abuse Linked to Impaired Cognitive and Motor Skills Despite Recovery of Dopamine Transporters

By Patrick Zickler, *NIDA NOTES* Staff Writer



Brain images of a person who has never used methamphetamine (left) and of a methamphetamine user after 1 month of abstinence (center). Lighter colors show distribution of dopamine transporters (DAT) in the striatum. DAT distribution is reduced in striatum of methamphetamine user. Brain image of a methamphetamine user after 14 months' abstinence (right) shows substantial recovery of DAT in striatum. Low levels of DAT in methamphetamine users were associated with poorer performance on tests of memory and motor skills, which did not improve with DAT after lengthy abstinence.

Animal studies have demonstrated that methamphetamine, a highly addictive stimulant, damages brain cells involved in transport of the chemical messenger dopamine. Now, NIDA-supported researchers have found that long-term methamphetamine abuse by humans is associated with a reduction in dopamine transporters after 2 months' abstinence from methamphetamine and that this damage appears to be linked to slowed motor skills and weakened memory. Methamphetamine abusers who were retested after remaining abstinent for at least 9 months showed substantial recovery from damage to the dopamine transporters but not from impairments in motor skills and memory.

Dopamine Transporter Damage After Brief Abstinence

Dr. Nora Volkow and colleagues at the Brookhaven National Laboratory in Upton, New York, and at the University of California, Los Angeles, used brain imaging studies and tests of motor skills and memory to investigate the effects of methamphetamine in 15 former methamphetamine abusers. The participants (nine women and six men, average age 32 years) had used the drug at least 5 days per week for at least 2 years, and had been abstinent from methamphetamine for at least 2 months.

The researchers used positron emission tomography (PET) to measure levels of dopamine transporters in the brain. PET imaging detects signals from chemical "tracers" that are injected into the bloodstream and carried to the brain, where they bind to dopamine transporters. The strength of the signals indicates the number of transporters. Compared with participants who never used the drug, methamphetamine abusers had an average reduction of 24 percent in levels of dopamine transporters (DAT) in the striatum, a part of the brain associated with control of movement, attention, motivation, and reward.

Participants also took a series of tests to assess brain functions associated with the striatum: fine motor skills (inserting pegs into angled holes as quickly as possible), gross motor skills (walking as rapidly as possible in a straight line), and memory (learning and recalling a list of unrelated words immediately, after a delay, and after a distraction). "The abstinent methamphetamine abusers showed impaired memory and slowed motor skills that were directly proportional to the deficits in DAT. The lower the levels of DAT, the worse their performance," Dr. Volkow says.

"The reduction of dopamine transporters was seen in all of the abusers," Dr. Volkow says. "DAT loss also occurs with age at a rate of 6 to 7 percent per decade, so the DAT losses in methamphetamine abusers are roughly equivalent to 40 years of aging." Furthermore, she says, DAT reduction in the range of 40 to 90 percent is one characteristic of Parkinson's disease, a progressive neurodegenerative disorder that causes tremor, weakness, and—in some patients—cognitive impairment. "There is a concern that methamphetamine abusers may be at increased risk for neurodegenerative disease as they age. This will depend

in part on the reversibility of DAT losses induced by methamphetamine abuse."

Dopamine Transporter Recovery

To assess the persistence of methamphetamine-related DAT loss and impairments, the researchers reevaluated five study participants (three women and two men, average age 29 years) after they had abstained from taking the drug for at least 9 months. While these participants' DAT levels had increased to roughly equal those of never-users of methamphetamine, they performed no better than

Methamphetamine abusers may be at increased risk for neurodegenerative disease as they age.

before on tests of gross and fine motor skills and memory. Additional evaluations of five other former methamphetamine abusers with 9 months or more of abstinence (four women and one man, average age 35 years) produced similar findings: normal DAT levels but reduced motor and cognitive skills.

"This study documents significant recovery of DAT with protracted abstinence from methamphetamine," Dr. Volkow says. "Moreover, for those evaluated twice, the longer the interval between the first and second evaluations, the larger the increases in DAT. This suggests that recovery is related to the length of time that methamphetamine abusers can stay off the drug. But, although there is a recovery in DAT levels, there is no parallel improvement in function."

The relationship between impaired function and DAT loss and recovery is unclear. It is possible that the DAT recovery is due to increased branching of dopamine terminals rather than increased numbers of terminals, Dr. Volkow says. "This may be insufficient to compensate for lost terminals. It is also possible that the neuropsychological functions require other brain systems that recover slowly or not at all from the effects of methamphetamine. Or the failure to find an unambiguous association between DAT recovery and improved function might reflect the small number of participants who were able to stay drug free. We will need longer term studies to see if increases in DAT over longer periods of time are sufficient for complete recovery of function."

Sources

- Volkow, N.D., et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *American Journal of Psychiatry* 158(3):377-382, 2001.
- Volkow, N.D., et al. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *Journal of Neuroscience* 21(23):9414-9418, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 6 (February 2002)

Annual Survey Shows Teen Smoking Down, Rise in MDMA Use Slowing

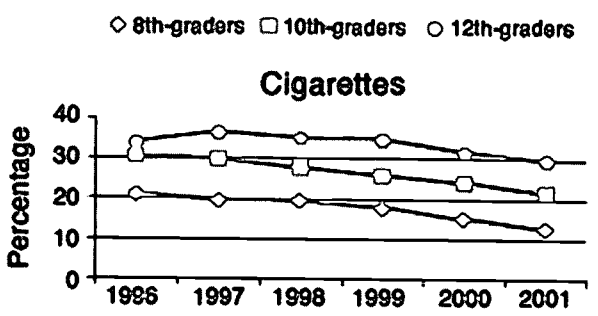
Use of cigarettes by American teenagers decreased from 2000 to 2001, according to the annual Monitoring the Future Study. Smoking was down for 8th- and 10th-graders, continuing a general pattern of declines seen among these students and 12th-graders since 1997.

Overall illicit drug use by teenagers in 2001 was essentially unchanged from rates reported in 2000, the study found. Among 8th-graders, 11.7 percent said they had used some illicit drug within the preceding month, and 19.5 percent said they had used within the preceding year. Among 10th-graders, 22.7 percent reported past-month use and 37.2 percent reported past-year use. One in four high school seniors (25.7 percent) reported past-month use; 41.4 percent of seniors said they had used an illicit drug in the preceding year. Use of any illicit drug has remained stable among 10th- and 12th-graders since its recent peak in 1997, but among 8th-graders the rate in 2001 is lower than that reported for 1996.

In 2001, 12.2 percent of 8th-graders—down from 14.6 percent in 2000—said they had used cigarettes in the preceding month. Among 10th-graders, past-month smoking decreased from 23.9 percent in 2000 to 21.3 percent in 2001. Smoking among high school seniors fell slightly, to 29.5 percent in 2001 from 31.4 percent the year before.

Although more teens in grades 8 (1.8 percent), 10 (2.6 percent), and 12 (2.8 percent) reported past-month use of MDMA (ecstasy) in 2001 than in 2000, the increases were generally not as steep as in the preceding 2 years and were not statistically significant.

Trends in Past-Month Use of Cigarettes



Among 8th-graders, 12.2 percent reported past-month cigarette use in 2001; this is the lowest rate reported since researchers began gathering smoking data on teenagers in 1991.

"It is encouraging that the trend toward more widespread use of MDMA in 1999 and 2000 appears to have slowed last year," says NIDA Acting Director Dr. Glen Hanson. "The 2001 survey data also show that greater numbers of high school seniors—nearly half of them, in fact—say they believe there is a great risk in using MDMA. We hope that NIDA's efforts to provide science-based information about the risks of drugs will contribute to further decrease in drug use."

Although patterns of illicit drug use by teens were largely unchanged in 2001, trends for use of some drugs showed significant change from 2000 to 2001:

- Steroids: Among high school seniors, past-month use increased from 0.8 to 1.3 percent, and past-year use increased from 1.7 to 2.4 percent.
- Heroin: Past-year use by 10th-graders decreased from 1.4 to 0.9 percent. Among seniors, past-year use decreased from 1.5 to 0.9 percent, and past-month use decreased from 0.7 to 0.4 percent.
- LSD: Past-month use by seniors increased from 1.6 to 2.3 percent, but past-year use by 10th-graders declined from 5.1 percent to 4.1 percent.

Monitoring the Future

The Monitoring the Future Study, funded by NIDA, is conducted by the Institute for Social Research at the University of Michigan in Ann Arbor. Data in the 2001 survey represent responses from more than 44,000 students in 424 schools across the Nation to questions about lifetime use, use during the past year, use during the past month, and daily use of various illicit drugs, alcohol, cigarettes, and smokeless tobacco. The survey also asks students about their perception of the risks associated with drugs.

Additional information about the Monitoring the Future Study can be obtained from NIDA Infofax at 1-888-NIH-NIDA (644-6432) or from NIDA's home page at www.drugabuse.gov. Information is also available from the University of Michigan's Monitoring the Future home page: monitoringthefuture.org. Information about MDMA (ecstasy) is available at the NIDA club drugs Web site, www.clubdrugs.org, and about steroids at NIDA's steroid abuse Web site: www.steroidabuse.org. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 5 (December 2001)

Using Science To Counter the Spread of Ecstasy Abuse

By NIDA Director Alan I. Leshner, Ph.D.

At a time when the abuse of most illicit drugs has leveled off or declined slightly among the Nation's youth, one drug has soared in popularity. It is known by many names, among them "MDMA," "ecstasy," "X," or simply "E." (See "MDMA/Ecstasy-A Drug With Complex Consequences") MDMA (3,4-methylenedioxymethamphetamine) is the only drug whose use has increased significantly among the Nation's 10th- and 12th-graders during each of the last 2 years. Last year it extended its reach to younger adolescents as use increased among eighth-graders. Recent epidemiologic data indicate that MDMA abuse also is spreading beyond its base of youthful users who attend dance clubs or all-night parties called "raves." Increasingly, Americans of all ages, social classes, and sexual orientations are using the drug in diverse social settings throughout the country.

We already have amassed a considerable body of scientific knowledge about the dangers of MDMA.

In 1999, NIDA mounted its Club Drug Initiative to respond to recent increases in the abuse of MDMA and other drugs, such as gamma-hydroxybutyrate (GHB), Rohypnol, ketamine, and methamphetamine. The ongoing initiative seeks to increase awareness of the dangers of these drugs among teens, young adults, parents, and communities. NIDA is supporting a broad range of animal and human studies on MDMA and other club drugs. The goal of those studies is to provide scientific information about the nature and extent of club drug abuse, the biological and behavioral effects of the drugs, and the personal and public health consequences of their abuse.

Some of the early fruits of NIDA's club drug research, along with the findings of international experts who have been studying MDMA for years, were featured at NIDA's scientific conference, "MDMA/Ecstasy Research: Advances, Challenges, Future Directions," at the National Institutes of Health in Bethesda, Maryland, in July. The conference highlighted the advances research has made in understanding MDMA and addressing the many questions we still must answer to develop prevention and treatment approaches to stem the abuse of this drug. (See "NIDA Conference Highlights Scientific Findings on MDMA/Ecstasy.")

Research clearly shows a pervasive perception among users that MDMA is a "fun" drug with minimal risks. We know that people are more likely to use a drug if they think they have nothing to lose by doing so. Thus, the myth that ecstasy is a benign drug that exacts virtually no price for its euphoric effects may at least in part be driving the widespread increases in the drug's abuse. This dangerous misperception challenges the drug abuse research, treatment, and prevention community to identify the true costs of using ecstasy and convey this information in ways that will effectively reduce abuse.

We already have amassed a considerable body of scientific knowledge about the dangers of MDMA. This drug can produce significant increases in heart rate and blood pressure that can last for several hours. MDMA abusers commonly take multiple tablets within brief time periods, often along with other commonly abused substances, such as alcohol, and while dancing for extended periods in hot and crowded conditions. These factors can dangerously increase MDMA's toxicity and lead to dehydration, hyperthermia, seizures, and heart or kidney failure. In fact, we have seen a nearly 18-fold increase in MDMA-related emergency room incidents from 1994 to 2000 reported by the Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network.

Research presented at the conference suggests some users dismiss the potential medical consequences because they do not often witness them. A pilot ethnographic study by researchers at Wright State University School of Medicine in Dayton, Ohio, indicates that ecstasy users in Central Ohio see a disjunction between media messages about the dangers of MDMA use and what people in their social networks tell them about their experiences with the drug. As a result, they feel they can use MDMA casually with few problems beyond a possible increase in anxiety, depression, and restlessness that some users experience a day or two after using the drug.

MDMA users may not think that transient mood disturbances are too high a price to pay for MDMA's euphoric effects. However, those symptoms provide a warning that potentially serious underlying brain damage is occurring. Increasingly, studies show that regular MDMA use causes long-lasting damage to brain cells that contain a critical neurotransmitter, serotonin, which helps regulate mood, pain, appetite, and sleep.

NIDA also is supporting prevention research to develop effective approaches that can address the entire spectrum of MDMA users.

Studies have associated MDMA use with loss of the serotonin-synthesizing enzyme tryptophan hydroxylase, depletions in serotonin content in tissue, and decreases in the structural component of serotonin neurons that enables the cells to convey signals. We do not yet know if the alterations are permanent, but we do know that they can persist for many years in animals and may be equally long-lasting in people. The consequences of such damage may include memory impairments, disrupted sleep cycles, mood disorders such as depression, and persistent anxiety, particularly among moderate to heavy MDMA users. As ongoing research provides more information about MDMA, NIDA is using all means of dissemination to keep the Nation up to date. This past spring, we teamed with the award-winning PBS series for teens, "In the Mix," to develop a television show on ecstasy. "Ecstasy" first aired last April and is regularly rebroadcast in all major markets of the country on more than 90 PBS stations with an audience of more than 1 million viewers.

In the last 2 years, our ongoing Club Drug Initiative has mailed a Community Drug Alert Bulletin on MDMA and other club drugs to nearly half a million physicians, treatment providers, nurses, and other clinicians; made English and Spanish fact sheets on MDMA available through our fax-on-demand service, NIDA Infofax; and distributed colorful postcards showing a brain scan of dramatic changes that linger in the brain's serotonin system weeks after MDMA is used. The cards are popular with young people and encourage them to contact NIDA for facts about MDMA. Current information on MDMA can be found at www.clubdrugs.org. NIDA also is supporting prevention research to develop effective approaches that can address the entire spectrum of MDMA users. Our research recognizes the need for prevention interventions aimed at different groups of MDMA users, such as men who have sex with men, ethnically diverse urban youths, and predominantly white heterosexual users in the Midwest. (See "The Many Faces of MDMA Use Challenge Drug Abuse Prevention.")

We have learned a lot about MDMA, the people who abuse it, and the short- and long-term consequences of such abuse. These answers—and those still to come from ongoing NIDA-supported research—will provide a solid foundation for the public policy, prevention, and treatment responses that will enable us to stem the abuse of MDMA and reduce its potentially devastating health consequences. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

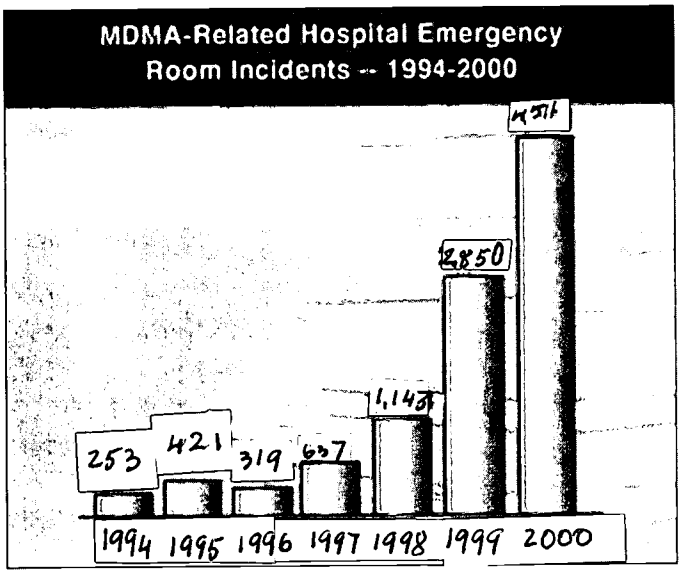
Research Findings

Volume 16, Number 5 (December 2001)

NIDA Conference Highlights Scientific Findings on MDMA/Ecstasy

By Robert Mathias and Patrick Zickler, *NIDA NOTES* Staff Writers

In the face of worldwide increases in the use of MDMA, or ecstasy, particularly among teens and young adults, NIDA convened an international array of scientists at the National Institutes of Health in Bethesda, Maryland, in July for a conference on "MDMA/Ecstasy Research: Advances, Challenges, Future Directions." MDMA researchers from Australia, Europe, and all regions of the United States detailed the latest findings on patterns and trends of MDMA abuse, its complex acute effects on the brain and behavior, and the possible long-term consequences of its use.

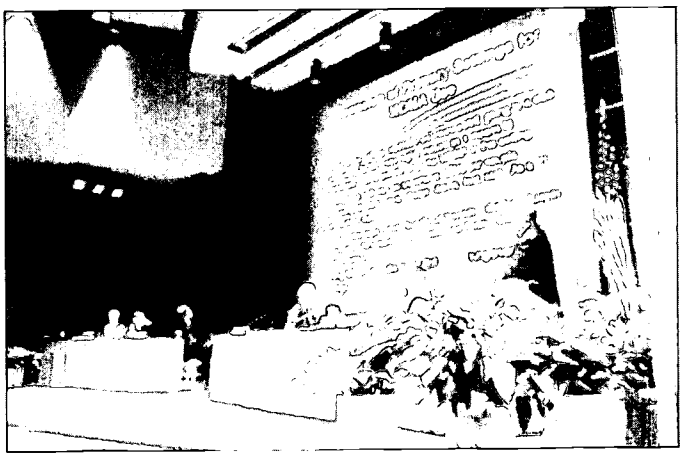


In opening remarks, Dr. Glen Hanson, director of NIDA's Division of Neuroscience and Behavioral Research, noted the tremendous interest of the scientific community and the general public in MDMA and its effects. The sold-out conference drew an audience of 565 people with a broad range of interests and perspectives. They included scientists, drug abuse prevention and treatment practitioners, clinicians, educators, high school counselors, and representatives from Federal and local public health departments and agencies.

A public health perspective on MDMA by James N. Hall, of the Up Front Drug Information Center in Miami, Florida, provided a sharp contrast to the prevailing public view of MDMA as an innocuous drug. MDMA use began to expand rapidly in the United States in 1996 with "more pills going to younger populations," Mr. Hall said. This upsurge in use led to an increase in drug-related problems. For example, MDMA-related hospital emergency room incidents increased from 253 in 1994 to 4,511 in 2000, according to recent data from the Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network. "Most of these emergency room mentions are multiple-drug cases," Mr. Hall said, "as polydrug use has become the norm."

The common practice of using MDMA in conjunction with other drugs was just one of several recurring themes sounded during a conference session on current trends and patterns of MDMA use. Other significant themes were:

- MDMA now is being used in urban, suburban, and rural areas throughout the country;
- MDMA continues to be used in its traditional settings of all-night dance parties, called "raves," and nightclubs; use also is common now on college campuses and at small group gatherings, such as house parties;
- MDMA is used by all ages but still mainly by adolescents and young adults; use has increased sharply in this population in recent years;
- MDMA users are predominantly white, but ethnically and racially diverse groups of people are now using the drug (see "The Many Faces of MDMA Use Challenge Drug Abuse Prevention"); and
- MDMA's euphoric effects can lead to unplanned or unwanted sexual contact that increases the risk of transmitting HIV/AIDS and other infectious diseases.



Researchers present the latest findings at NIDA's international conference on MDMA/ecstasy abuse.

Acute Effects of MDMA

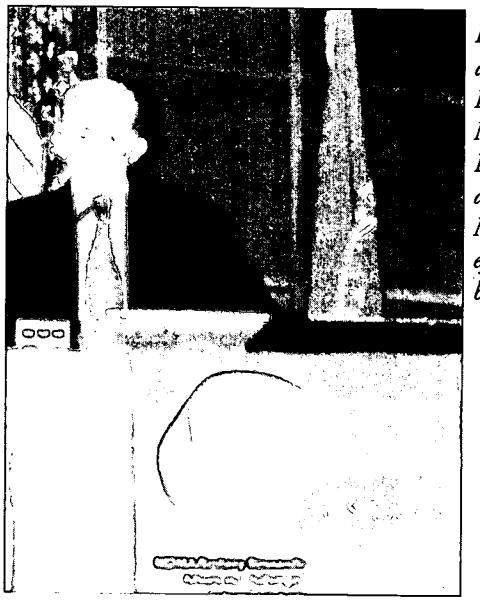
A session on MDMA's acute effects presented the latest findings on how the drug works in the brain and body to produce its perceptual and physiological impact. The session explored the interaction of underlying biological and behavioral factors and mechanisms that may contribute to the possibly harmful effects of MDMA use.

Animal studies have indicated that MDMA increases extracellular levels of the chemical messengers serotonin and dopamine. In laboratory studies to understand how these increases affect humans, Dr. Manuel Tancer of Wayne State University in Detroit asked participants to compare MDMA's effects to those produced by compounds that stimulate serotonin alone and dopamine alone. MDMA's effects were reported to resemble some features of both compounds, noted Dr. Tancer. This indicates that both the dopamine and serotonin systems play a role in producing MDMA's subjective effects in humans.

MDMA also has powerful acute physiological effects in humans that increase with larger doses, according to several presentations. MDMA's cardiovascular effects include large increases in blood pressure, heart rate, and myocardial oxygen consumption, noted Dr. John Mendelson of the University of California, San Francisco. MDMA's elevations of heart rate and blood pressure were comparable to those produced by a maximal dose of dobutamine, a cardiovascular stimulant used in stress tests to evaluate patients for coronary artery disease, he said. However, unlike dobutamine, MDMA did not increase the heart's pumping efficiency. Thus, MDMA-induced heart rate and blood pressure increases may lead to an unexpectedly large increase in myocardial oxygen consumption, which can increase the risk for a cardiovascular catastrophe in people with preexisting heart disease, he said.

Even small increases in MDMA dose can greatly reduce the body's ability to metabolize the drug. This means MDMA is not processed and removed from the body quickly and remains active for longer periods. "As a result, plasma levels of the drug and concomitant increases in toxicity may rise dramatically when users take multiple doses over brief time periods. Increased toxic effects can lead to harmful reactions such as dehydration, hyperthermia, and seizures," Dr. Mendelson said. Drugs such as methamphetamine that are commonly abused in conjunction with MDMA also may increase the cardiovascular effects of MDMA, he said.

MDMA tablets often contain other drugs, such as ephedrine, a stimulant, and dextromethorphan, a cough suppressant that has PCP-like effects at high doses, that also can increase its harmful effects. In addition, drugs sold as MDMA may actually be substances that are much more dangerous, according to Dr. Rodney Irvine of the University of Adelaide in Australia. For example, the hallucinogen PMA (4-methoxyamphetamine), which is similar in some respects to MDMA, has even more severe toxic effects on the cardiovascular system, particularly as dosage increases. The drug has been sold as MDMA in Australia and has been associated with a number of deaths. PMA is now being distributed in the United States and has been linked to deaths in Chicago and Central Florida, according to the Federal Drug Enforcement Administration.



Dr. Glen Hanson, director of NIDA's Division of Neuroscience and Behavioral Research, describes some of MDMA's toxic effects on different brain regions.

Long-Term Effects of MDMA

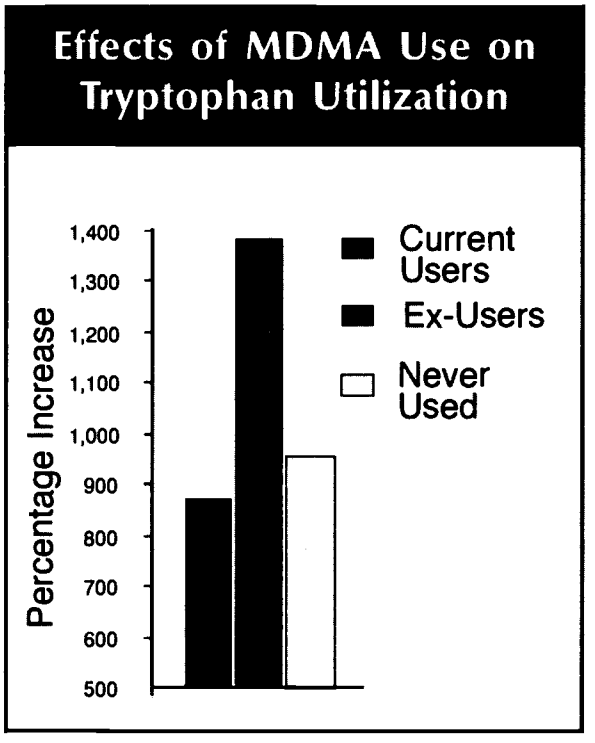
During the second day of the conference, researchers from the United States and other countries described current investigations of ecstasy's long-term effects. Introducing the day's program, Dr. Hanson summarized the mechanisms thought to be responsible for MDMA's toxic effects on the brain's serotonin system. In tests of learning and memory, he noted, MDMA users perform more poorly than nonusers on tasks associated with brain regions affected by MDMA. Higher doses of MDMA appear to be associated with more profound effects, and the consequences may be long-lasting.

Dr. Charles Vorhees of Children's Hospital Medical Center in Cincinnati, Ohio, has found that, in rats, exposure to MDMA during a period of brain development that corresponds to human brain development during the trimester before birth is associated with learning deficits that last into adulthood. "The impairment, which affects the rate at which the animals learn new tasks, increases in severity as the dose of MDMA increases and is more pronounced as the tasks become more complex," Dr. Vorhees said.

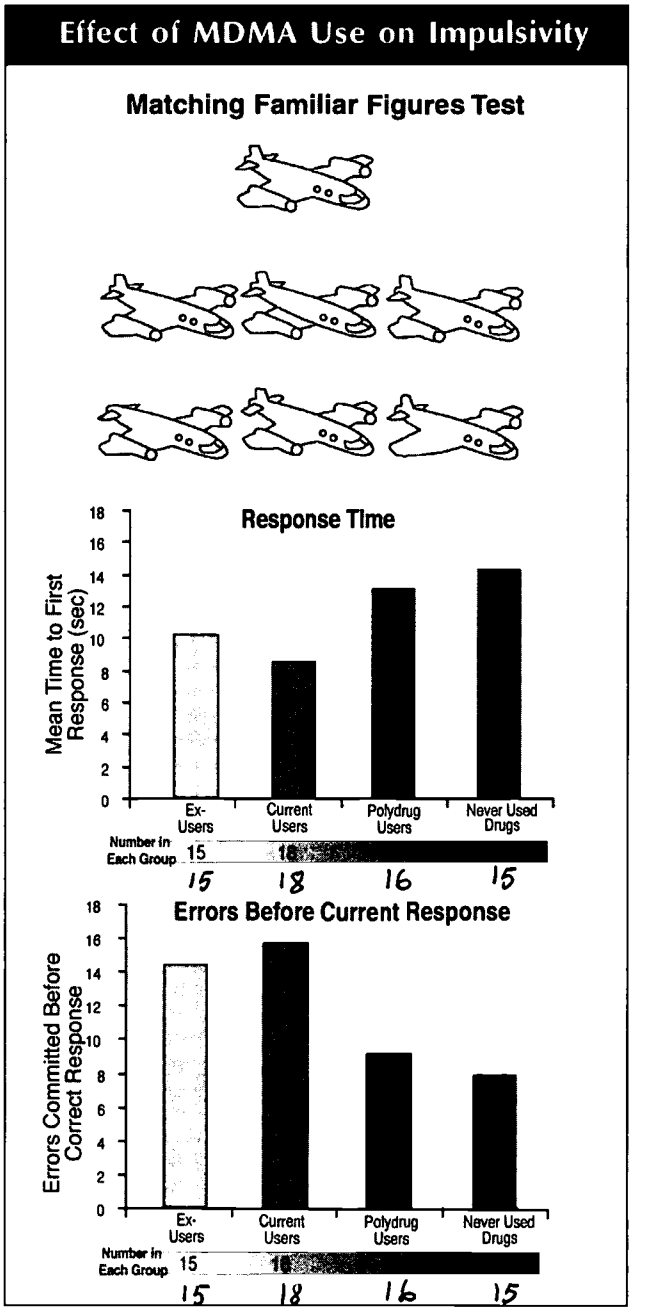
These findings of MDMA's effects on brain development are limited to studies involving rats, but there is a growing body of research suggesting that—in adult primates—MDMA can cause long-lasting damage. At the Johns

Hopkins University School of Medicine in Baltimore, Drs. Una McCann, George Ricaurte, and other investigators have found that exposure to MDMA is associated with damage to brain cells that release serotonin; this damage persists for at least 7 years in nonhuman primates. In humans, the researchers have found that MDMA use is associated with verbal and visual memory problems in individuals who have not used the drug for at least 2 weeks. "We see a relationship between the dose of MDMA and the severity of the effects. In animals, MDMA-induced damage is extensive and long-lasting and we do not yet know if it is reversible," Dr. Ricaurte said. "A person who takes enough of the drug to feel its effects is taking enough to be at serious risk of similar damage to the brain and to memory and learning."

Dr. Linda Chang, a scientist at the Brookhaven National Laboratory in Upton, New York, reported on research using brain imaging techniques to evaluate the effects of occasional use of MDMA. She and her colleagues Dr. Charles Grob and Dr. Russell Poland at the University of California, Los Angeles, used single photon emission computed tomography to evaluate blood flow to the brain—which is regulated in part by serotonin—in 21 MDMA users who had taken the drug at least 6 times per year for more than 1 year (on average, a total of 75 times), but had not used the drug in at least 2 weeks (4 months average abstinence). The participants then were given MDMA in two sessions over the course of a week. Two weeks later, brain images showed decreased blood flow compared to the earlier images. The decrease was greater in those individuals who had higher total use of the drug.



MDMA disrupts brain processes that use the amino acid tryptophan to make the neurotransmitter serotonin, which affects memory and mood. Five hours after drinking a tryptophan supplement, ex-users of MDMA showed greater elevations of their blood tryptophan levels than did current users or nonusers, indicating that less of the amino acid had been converted to serotonin.



The airplane figure at top is exactly matched by only one of six similar figures below. When asked to find the correct match, current and ex-users of MDMA made quicker choices and made more wrong choices before identifying the correct match than participants who used drugs other than MDMA or who used no drugs at all.

MDMA Research in Europe

The popularity of MDMA as a "club drug" began in Europe in the late 1980s—roughly 5 years earlier than in the United States—and researchers there have studied the drug's effects in populations with a longer history of drug use. In Great Britain and Germany researchers have found that MDMA users—and even former users who have not taken the drug for at least 6 months—perform more poorly on some tests of memory and learning than do nonusers. MDMA also is associated with psychological problems such as anxiety and depression, this research suggests.

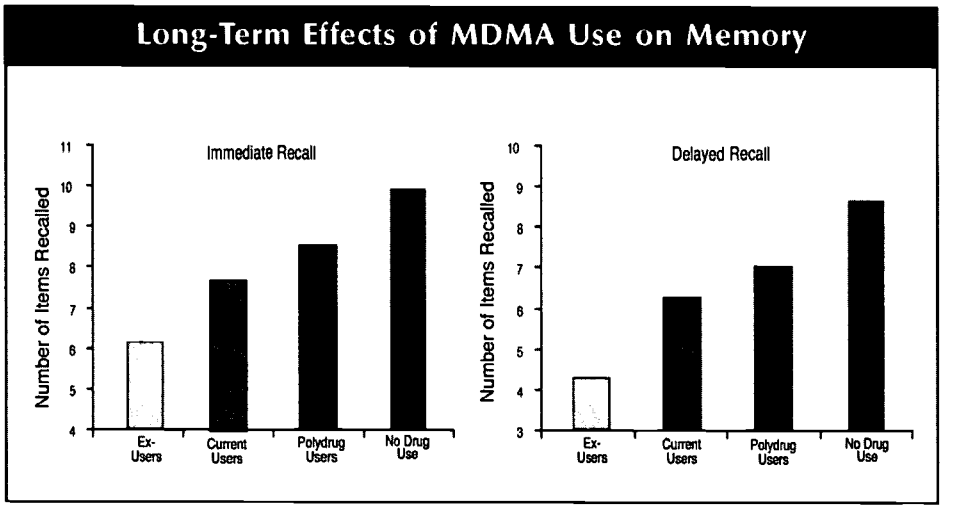
The learning and memory functions that appear to be impaired by MDMA in animal and human studies are associated with the brain's serotonin system. The specific effects of MDMA can be evaluated directly in animal studies, but in humans nearly all MDMA users also use other drugs such as marijuana, cocaine, and alcohol. In an effort to more fully understand how MDMA affects polydrug users, Dr. Valerie Curran and her colleagues at University College London investigated the effect of MDMA use on the body's ability to use tryptophan, an amino acid that is one of the chemical building blocks for serotonin. The research involved three groups of polydrug users: some were current MDMA users, some had stopped using the drug, and some had never used it.

The researchers first measured blood levels of tryptophan and found that current and ex-users of MDMA had higher blood levels than did nonusers and that the levels were elevated in proportion to the total amount of drug the participants had used. The investigators then gave participants drinks that contained augmented amounts of tryptophan in addition to all other necessary amino acids. Five hours later they measured blood levels of the amino acid. Ex-users of MDMA showed far higher levels of tryptophan in their blood than did nonusers or current users, Dr. Curran said. "Tryptophan should cross the blood-brain barrier to be incorporated into the biosynthesis of serotonin, but in ex-users, significantly higher levels of tryptophan remained in the blood," she said.

In memory tests, current users did more poorly than did nonusers; ex-users-who had not taken MDMA for an average of 2 years-had the poorest performance. The reason for such poor performance among the ex-users is uncertain, Dr. Curran said. One possibility is that these were people who developed particularly severe adverse effects and quit using the drug because of them. "Whatever the reason, there is a clear correlation between a biological marker (blood levels of tryptophan), a functional deficit (poor performance on tests of memory), and the total dosage and length of time these people used MDMA before they stopped," Dr. Curran said.

Dr. Euphrosyne Gouzoulis-Mayfrank of the University of Technology in Aachen, Germany, also described research involving MDMA's effects on polydrug users. She and her colleagues compared cognitive performance in three groups of participants age 18 to 30. One group included MDMA users with a typical pattern of recreational use (at least twice per month within the preceding 2 years) who also used marijuana (at least once per month over a 6-month period), a second group who did not use MDMA but whose marijuana use roughly matched that of the MDMA users, and a third group who had never used either drug. "Ecstasy users showed no impairment in tests of alertness," she said, "but performed worse than one or both control groups in more complex tasks of attention, in memory and learning tasks, and in tasks reflecting aspects of general intelligence."

Dr. Michael Morgan of the University of Sussex in Great Britain described research that suggests a relationship between marijuana use, MDMA use, and psychological problems and memory deficits. Dr. Morgan and his colleagues studied the effects among groups of current MDMA users, ex-users, polydrug users who did not use MDMA, and participants who had never used drugs.



In tests of MDMA effects on memory, ex-users and current users performed worse than participants who used drugs other than MDMA or used no drugs. Ex-users, in particular, showed greatly impaired memory.

The researchers found that the psychological measures were more closely associated in the polydrug population with current marijuana use than with past MDMA use. "Overall, however, current and ex-users of MDMA have dramatically higher measures of psychopathology such as impulsivity than nonusers," Dr. Morgan said. Like Dr. Curran, Dr. Morgan found cognitive deficits associated with rates of past MDMA use. In tests of memory, both current and ex-users performed more poorly than nonusers. He also found that on some tests ex-users performed worse than did current users, although he noted that the reasons for poorer performance by ex-users could not clearly be linked exclusively to MDMA use. "Nonetheless, as a practical matter, ex-users show massively impaired memory. Not only had they not recovered, they were actually worse than current users," Dr. Morgan said. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 5 (December 2001)

The Many Faces of MDMA Use Challenge Drug Abuse Prevention

By Robert Mathias, *NIDA NOTES* Staff Writer

Three NIDA-funded ethnographic studies presented at the MDMA/Ecstasy Conference illustrate the diversity and complexity of MDMA use in the United States. The studies showed both similarities and differences in patterns of MDMA use and associated sexual behaviors among homosexual men in Boston and New York City, predominantly white heterosexual users in central Ohio, and a racially diverse group of users in Hartford, Connecticut. The studies employed a variety of research techniques, such as on-site observation and interaction with ecstasy users in clubs, informal and structured interviews, and small focus groups, to ascertain who uses MDMA, their patterns of drug use and related behaviors, and the settings in which they use drugs.

Preliminary findings from these studies suggest that targeted drug abuse prevention approaches that address specific factors that are associated with MDMA use by different types of users and in different regions of the country are needed to reduce MDMA abuse. Further research to understand the factors that increase or reduce the risks for drug use in these groups is needed to shape prevention initiatives, the researchers indicated.

MDMA Use Among Men Who Have Sex With Men

A field study conducted by Dr. Patricia Case of Harvard Medical School in Boston found considerable individual, group, and regional variations in patterns of MDMA use among club-drug-using men who have sex with men (MSM) in Boston and New York. More than 50 percent of men interviewed in the study frequently used MDMA in combination with other drugs and 11 percent had injected mainly anabolic steroids within the last 3 months. MSM reported that MDMA use usually occurs with other drugs, including ketamine, cocaine, methamphetamine, and Viagra. Some users primarily engage in uncontrolled drug use, others also take MDMA frequently but according to a set schedule with other drugs to achieve special effects, and still others use MDMA occasionally in connection with special circumstances or holidays.

The MSM in this study were very sexually active and reported unprotected sex while using MDMA although not so often as with other drugs, such as methamphetamine. MDMA prevention messages have had little effect on MSM. This population expressed more concern about the risks of GHB (gamma-hydroxybutyrate), a central nervous system depressant, because of reported overdose deaths from that drug in both cities.

MDMA Use in Central Ohio

Dr. Robert Carlson and colleagues of Wright State University School of Medicine in Dayton, Ohio, conducted a pilot study of MDMA use among 28 individuals in 2 focus groups in Dayton and Columbus. Participants were evenly divided between men and women who were almost exclusively heterosexual. Like the MSM study, the Ohio study showed tremendous variations in patterns of MDMA use.

One-third of the study population said they had used other club drugs, such as ketamine and GHB, and high alcohol use was common. Dance clubs were popular settings for MDMA use among college students and other young adults, who tended to use MDMA to enhance sociability. MDMA users at raves were younger, less educated, and more likely to have a drug-using lifestyle than were the club-goers. Participants said they also used MDMA at parties, lakes, beaches, high schools, and in cars.

"MDMA is seen as a relatively benign drug," Dr. Carlson said. "Most people hear of very few negative consequences from friends, although they do express concern about adulterants in the pills they are getting." None of the participants reported any negative effects of MDMA use on memory, cognition, or work performance. Condom use during sex appeared to be the norm, but several women reported having sex with men they had not intended to be with after taking MDMA.

MDMA Use Among Urban Youth in Hartford, Connecticut

Dr. Jean Schensul, of the Institute for Community Research in Hartford, Connecticut, reported information from observations and interviews with urban youths in party and club settings combined with survey data obtained during a 15-month study of youths in Hartford. Study participants were 16 to 24 years old, 70 percent male, 40 percent Hispanic, 38 percent African American, and 22 percent Caucasian, Asian, and mixed race or ethnicity. MDMA use in this population is linked to their social networks, club-going, and parties. MDMA is often used with other drugs, including marijuana, PCP, and alcohol.

"These youth have limited access to accurate sources of information and are uninformed about the risks of MDMA use and drug mixing," Dr. Schensul said. They are exposed to popular hip-hop magazines and rap music lyrics that promote the connection between ecstasy, the "good life," and better sex. The study shows that MDMA use has spread from the suburbs to the city and is increasing the already high levels of risk of unprotected sex and sexually transmitted diseases among these economically vulnerable young people. The findings suggest that culturally and developmentally appropriate prevention approaches that focus on reducing harmful behaviors are needed for this population, Dr. Schensul said. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 5 (December 2001)

MDMA/Ecstasy—A Drug With Complex Consequences

MDMA (3,4-methylenedioxymethamphetamine), also known as "ecstasy," is a complex drug that defies simple classification. Its chemical structure bears similarities to both the stimulant methamphetamine and the hallucinogen mescaline. As a result it can produce both stimulant and psychedelic effects, though the latter are milder than those produced by true hallucinogens, such as LSD. Mixed stimulant and psychedelic effects plateau after approximately 2 hours and can continue for up to 6 hours. Ecstasy's pleasurable effects can include enhanced sense of pleasure and self-confidence, increased energy, and feelings of peacefulness, acceptance, and closeness with others. Such effects help explain ecstasy's popularity with adolescents and young adults in the United States who began using it in increasing numbers during the 1990s, particularly at nightclubs and raves.

Research has shown that, in addition to its euphoric effects, MDMA can lead to disruptions in body temperature and cardiovascular regulation. Environmental conditions, such as the extremely high temperatures found at many dance venues, and the drug's stimulant effects can increase the severity of these symptoms. This combination of circumstances can lead to dehydration, hypertension, hyperthermia, and heart or kidney failure. MDMA also damages nerves in the brain's serotonin system and appears to produce long-term deficits in memory and cognition. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 5 (December 2001)

Methamphetamine, Cocaine Abusers Have Different Patterns of Drug Use, Suffer Different Cognitive Impairments

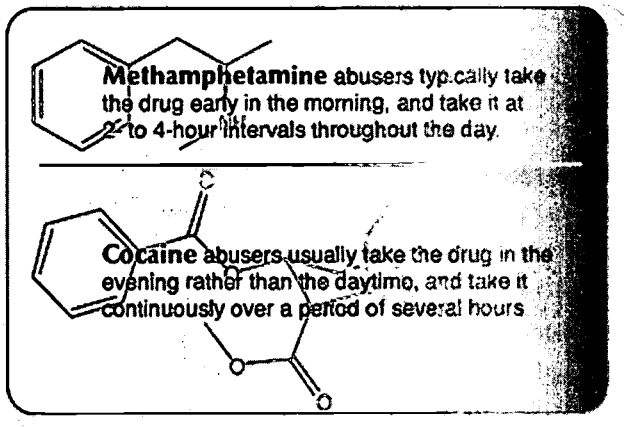
By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-supported research has found that methamphetamine abusers typically use the drug throughout the day in a pattern that resembles taking medication, while cocaine abusers often exhibit a binge pattern, using the drug continuously over a period of several evening and nighttime hours. And, according to the researchers at the University of California, Los Angeles (UCLA), the drugs appear to cause different types of deficits in reasoning and concentration.

Patterns of Use

Dr. Sara Simon and her UCLA colleagues interviewed 120 methamphetamine abusers and 63 cocaine abusers to determine patterns of drug use. Ninety-seven of the methamphetamine abusers and 56 cocaine abusers were recruited from treatment programs; the others were currently using the drug and not seeking treatment.

Continuous use—more than 20 times per month—was more common for both cocaine abusers (52 percent) and methamphetamine abusers (70 percent) than was any other pattern of drug use. Among those who used either drug fewer than 20 times per month, methamphetamine abusers were 4 times as likely as cocaine abusers (48 percent compared with 12 percent) to use the drug at least once per week in a regular cycle.



"The typical methamphetamine abuser reported using the drug when he or she first got up in the morning, then using approximately every 2 to 4 hours during their waking day. Most of the descriptions of use more closely resembled taking a medication than using a drug for pleasure," Dr. Simon says. "Cocaine abusers reported patterns that fit a picture of recreational use: They began in the evening and continued until all the cocaine on hand had been used."

The different patterns of use may in part be a result of the drugs' different effects in the body, the researchers say: Methamphetamine triggers the release of large amounts of the neurotransmitter dopamine into areas of the brain that regulate feelings of pleasure, whereas cocaine blocks the removal of dopamine, resulting in an accumulation that causes continuous pleasurable stimulation of brain cells. The effects of methamphetamine typically last more than 10 hours, and the half-life (the time it takes for the body to remove 50 percent of the drug) of methamphetamine is 12 hours. Cocaine's half-life is roughly 1 hour, and the drug's high lasts about 20 to 30 minutes.

Understanding the patterns of use for methamphetamine and cocaine will help treatment providers and drug users identify circumstances that may lead to relapse to drug use. "Differences in use patterns indicate different triggers and different times and places when the recovering abuser is particularly vulnerable," says Dr. Simon.

Effects on Reasoning and Memory

In another study, Dr. Simon and her colleagues evaluated the effects of methamphetamine and cocaine on learning and memory in 40 methamphetamine abusers and 40 cocaine abusers who were not in treatment and 80 individuals who had never used either stimulant drug. The researchers administered tests to evaluate memory, perceptual speed and ability to manipulate information, ability to ignore irrelevant information, general intelligence, verbal fluency, and executive function (abstract reasoning, reactive flexibility, and ability to use feedback).

Methamphetamine abusers performed more poorly than nonusers of stimulants in tests of word recall, perceptual speed, ability to manipulate information, and abstract thinking. Cocaine abusers scored more poorly than nonusers of stimulants in tests measuring ability to recall words and pictures and working memory.

"Methamphetamine abusers displayed impairments on the tests of perceptual speed and manipulation of information

that were not seen in the cocaine group. Moreover, in tests that require both speed and manipulation, there was even more difference between the groups than on tests of either skill separately," Dr. Simon says.

"Overall, both drugs are associated with similar cognitive deficits," Dr. Simon says. "The most striking difference is that methamphetamine abusers have more trouble than cocaine abusers at tasks requiring attention and the ability to organize information."

Sources

- Simon, S.L., et al. A comparison of patterns of methamphetamine and cocaine use. *Journal of Addictive Diseases,* in press.
- Simon, S.L., et al. Cognitive performance of current methamphetamine and cocaine users. *Journal of Addictive Diseases,* in press.

NN

23

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 2 (May, 2001)

Information on LSD, PCP, and Related Drugs Available in New Research Report

NIDA has issued a new report summarizing recent scientific research on hallucinogens and other mind-altering drugs that distort perceptions of reality. The eight-page Research Report, "Hallucinogens and Dissociative Drugs," describes the drugs, explains how they work, and details how they impair users' ability to think, act, and communicate. Following are highlights from the report:

What are hallucinogens?

Hallucinogens cause hallucinations, profound distortions in a person's perception of reality. Users see images, hear sounds, and feel sensations that seem real but do not exist. LSD (lysergic acid diethlyamide) is the most potent mood- and perception-altering drug known and the most widely used hallucinogen. Other hallucinogens, including mescaline, psilocybin, and ibogaine, have actions and effects similar to those of LSD.

NATIONAL INSTITUTE ON DRUG ABUSE

Research Report SERIES

HALLUCINOGENS AND DISSOCIATIVE DRUGS *Including LSD, PCP, Ketamine, Dextromethorphan*

Drugs with street names like acid, angel dust, and vitamin K distort the way a user perceives time, motion, colors, sounds, and self. These drugs can disrupt a person's ability to think and communicate rationally, or even to recognize reality, sometimes resulting in bizarre or dangerous behavior. Hallucinogens such as LSD cause emotions to swing wildly and real-world sensations to assume unreal, sometimes frightening aspects. Dissociative drugs like PCP and ketamine may make a user feel disconnected and out of control.

In addition to their short-term effects on perception and mood, LSD is associated with psychotic-like episodes that can occur long after a person has taken the drug, and PCP and ketamine can cause respiratory depression, heart rate abnormalities, and a withdrawal syndrome. Use of LSD and other hallucinogens by secondary school students has declined since 1998, but ketamine and LSD are becoming more widely used at dance clubs and all-night raves by older teens and young adults.

NIDA research is developing a clearer picture of the dangers of these mind-altering drugs. We have compiled the scientific information in this report to inform readers and to strengthen prevention and treatment efforts.

Alan I. Leshner, Ph.D.
Director
National Institute on Drug Abuse

from the director

What are hallucinogens?

Hallucinogens are drugs that cause hallucinations—profound distortions in a person's perceptions of reality. Under the influence of hallucinogens, people see images, hear sounds, and feel sensations that seem real but do not exist. Some hallucinogens also produce rapid, intense emotional swings.

Hallucinogens cause their effects by disrupting the interaction of nerve cells and the neurotransmitter serotonin. Distributed throughout the brain and spinal cord, the serotonin system is involved in the control of behavioral, perceptual, and regulatory systems, including mood, hunger, body temperature, sexual behavior, muscle control, and sensory perception.

LSD (an abbreviation of the German words for "lysergic

Psilocybin mushrooms and peyote cactus are plants that people have used to produce "visions."

U.S. Department of Health and Human Services • National Institutes of Health

What are LSD's effects?

LSD's effects typically are felt within 30 to 90 minutes after ingestion and may last as long as 12 hours. The drug's effects, which are unpredictable and vary with the user's personality, mood, expectations, and surroundings, may include:

- *Physiological effects:* Increased blood pressure and heart rate, dizziness, loss of appetite, dry mouth, sweating, nausea, numbness, and tremors.
- *Emotional effects:* Rapid shifts through a range from fear to euphoria, so the user seems to experience several emotions simultaneously.
- *Sensory effects:* Highly intensified colors, smells, sounds, and other sensations. Changing perceptions of sensations, so the person may seem to hear colors and see sounds.
- *Hallucinations:* Distortions or transformations in shapes and movements. Perceptions that time is moving very slowly or that the user's body is changing shape.
- *Long-term effects:* Persistent psychotic states, impairment of the capacity to recognize reality, think rationally, or communicate. Hallucinogen persisting perception disorder, commonly referred to as "flashbacks," which consists of spontaneous, repeated recurrences of some sensory distortions originally produced by LSD.

What are dissociative drugs?

Dissociative drugs, such as PCP (phencyclidine) and ketamine, were initially developed as general anesthetics. They distort perceptions of sight and sound and produce feelings of detachment but do not typically produce hallucinations.

What are the effects of PCP and ketamine?

PCP. In its common powdered form, PCP may be snorted or sprinkled on marijuana, tobacco, or parsley and smoked. Effects are felt within minutes of ingestion, may last for several hours, and are unpredictable. At low doses, physiological effects may include shallow, rapid breathing, increased blood pressure and heart rate, and elevated

temperature. At higher doses, dangerous changes can occur in blood pressure, heart rate, and respiration, often with nausea, blurred vision, dizziness, and decreased awareness of pain.

Ketamine. Available illegally in powder or pill form, ketamine is similar to, though less potent and shorter acting than, PCP. The drug is odorless and tasteless, induces amnesia, and cannot be detected in beverages. It is sometimes used in commission of sexual assaults referred to as "drug rape."

For More Information

Copies of the NIDA Research Report "Hallucinogens and Dissociative Drugs" may be ordered from the National Clearinghouse for Alcohol and Drug Information at 1-800-729-6686 or TDD 1-800-487-4889 for the deaf. Additional information on LSD, PCP, and other illicit drugs can be obtained through NIDA's Web site at www.drugabuse.gov. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 16, Number 2 (May, 2001)

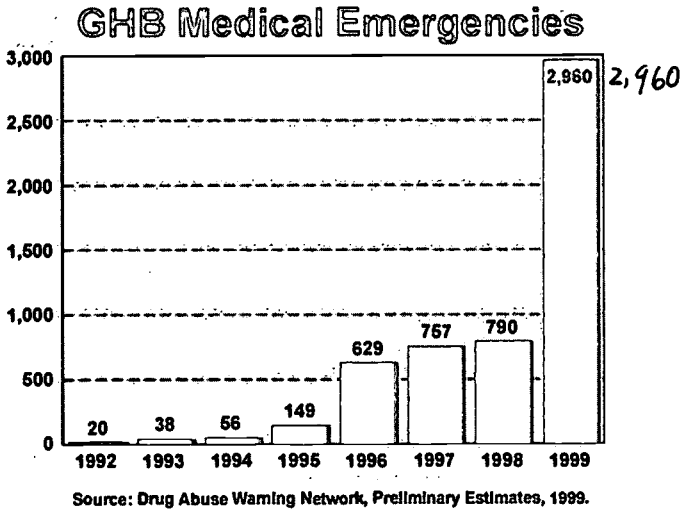
Conference Highlights Increasing GHB Abuse

By Lori Whitten, *NIDA NOTES* Contributing Writer

"We don't yet know if GHB abuse is a fad or if it will become an epidemic, but the knowledge exchanged at this conference will keep NIDA on top of the problem," said Dr. Jerry Frankenheim of NIDA's Division of Neuroscience and Behavioral Research (DNBR). Dr. Frankenheim served as chair of the day-long "All About GHB" conference held last summer. NIDA sponsored the meeting to share expert information about gamma-hydroxybutyrate (GHB), an increasingly abused, potentially lethal illegal drug.

Nearly 50 participants from around the world heard accounts of GHB distribution and acquisition, trends in GHB abuse, and information on the symptoms and treatment of GHB overdose. Participants discussed the basic science of GHB, including its biochemistry, behavioral neuro-pharmacology and toxicology, pharmacokinetics, physiological functions, and the potential medical uses of GHB. "This is the first time that epidemiologists, physicians, basic researchers, and representatives of law enforcement have met on the topics of GHB and the chemicals that can be converted to GHB by the body," said Dr. Minda Lynch of DNBR, a meeting co-chair.

GHB is a central nervous system (CNS) depressant and is most often abused in an attempt to feel euphoric, relaxed, and uninhibited. In the United States, GHB can be prescribed in a very low dose as an experimental treatment for narcolepsy, a sleep disorder, under tightly controlled conditions. However, those who abuse GHB (also known as "G" or "liquid ecstasy") may require emergency medical attention when they overdose or experience withdrawal symptoms.



The number of patients treated for GHB overdose or GHB-related problems in hospital emergency departments has increased sharply in the last 5 years.

Dr. Frankenheim said that few data are available yet on the relatively new problem of GHB abuse-the Government has tracked GHB use only since it was declared illegal in March 2000. GHB abuse is also difficult to monitor because the drug can be easily manufactured with recipes available on the Internet. Further, there is no simple diagnostic test for GHB that can be used in hospital emergency departments, so it often goes undetected.

GHB overdose can cause unconsciousness, slowed heart rate, respiratory depression, seizures, hypothermia, nausea, vomiting, and coma. The combination of coma and vomiting or coma and a blocked airway can be deadly. "GHB has several characteristics that increase the likelihood of toxicity," says Dr. Frankenheim. "A small increase in dose can push the sedative effects to a lethal level. High doses of GHB overwhelm the body's ability to eliminate the drug, and therefore lead to greater effects of longer duration than expected." GHB's purity and strength are especially difficult to determine because the drug can be made from a number of chemical formulas, which differ in the amount of GHB produced when metabolized by the user's body.

When GHB is ingested with other drugs, especially alcohol and other CNS depressants, its potential for deadly effects increases. GHB, usually in combination with alcohol, has been linked to more than 60 deaths, almost 60 percent of which were among people aged 20 to 29. The number of reported GHB-related deaths probably underestimates the true number, since GHB does not remain in the body very long and is usually not tested for at autopsy. In response to recent GHB-related emergencies as public health concerns, the Institute has issued a request for grant proposals to study GHB and its precursors. Through its GHB Antidote Initiative, NIDA is beginning the process of developing an antidote for GHB poisoning.

GHB and other club drugs are often abused by young people at all-night parties and "raves," but evidence indicates that GHB abuse is spreading beyond the club scene.

For example, bodybuilders have said they use GHB because it stimulates the release of growth hormone. Alcoholics may take GHB in an attempt to eliminate alcohol cravings, in spite of a lack of medical approval for this use in the United States. In some European countries, GHB is prescribed as a treatment for alcoholism.

The meeting also highlighted the criminal practice of covertly slipping GHB into a person's drink to make that person more susceptible to sexual assault. GHB and a similar drug, Rohypnol, are known as "date rape" drugs. Robert P. Mecir of the Bureau of Narcotic Enforcement Regional Office in San Jose, California, said that substances used for "drug rape"—a more accurate term than "date rape"—can render the victim helpless by causing a loss of muscle coordination, confusion, sedation, and amnesia.

The addictive potential of GHB is not yet known, but individuals who use GHB report that they must increase dosage to continue to attain euphoric and relaxing effects. Dr. Karen Miotto of the University of California, Los Angeles, described the severe withdrawal symptoms—extreme agitation, delirium, insomnia, tremor, rapid heart rate, and anxiety—experienced when chronic GHB use is discontinued. Some people who abuse GHB have difficulty reducing or discontinuing use.

"The public may mistakenly perceive GHB as a safe drug because it was only recently made illegal, was previously available in health food stores as a dietary supplement, is marketed over the Internet, and is prescribed for limited medical use," Dr. Frankenheim says. To combat this misconception, NIDA is providing science-based information about GHB and other club drugs to teens, young adults, parents, and communities. NIDA recently disseminated a special Community Drug Alert Bulletin and continues its efforts to educate the public about the dangers of club drugs. (See "NIDA Launched Initiative to Combat Club Drugs" and "A Club Drug Alert")

For More Information

NIDA's Club Drug Web site (www.clubdrugs.org) contains science-based information about GHB and similar drugs. NIDA Infofax fact sheets on GHB, Rohypnol, and other club drugs are free and can be ordered by phone, 1-888-644-6432 or TDD, 1-888-889-6432 for the deaf, and they are available on NIDA's home page on the Web at www.drugabuse.gov. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

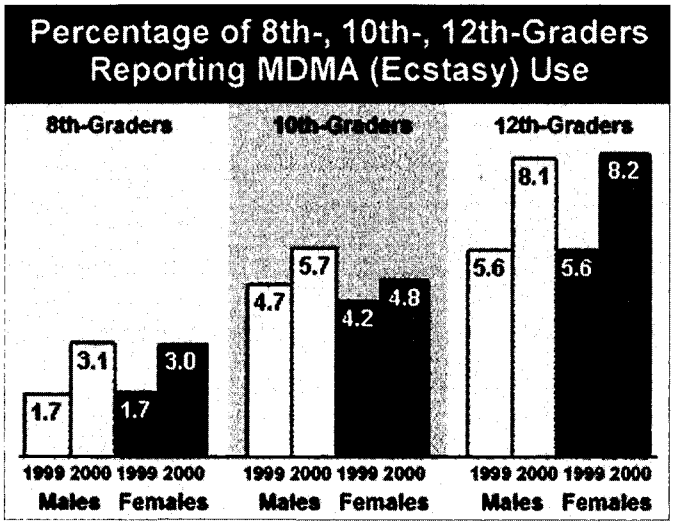
Research Findings

Volume 16, Number 2 (May, 2001)

Annual Survey Finds Increasing Teen Use Of Ecstasy, Steroids

By Patrick Zickler, *NIDA NOTES* Staff Writer

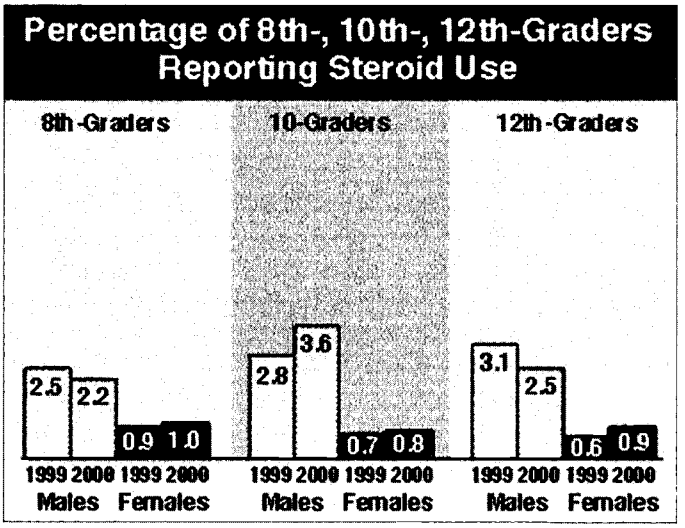
For the fourth year in a row, the percentages of 8th-, 10th-, and 12th-graders avoiding all use of illicit drugs remained level or increased in 2000, according to the 26th annual Monitoring the Future study. However, the nationwide survey of drug use among teenagers found that use of MDMA (ecstasy) has increased in all age groups and that use of steroids has risen among 10th-graders.



Graph on MDMA Trends in High School Children

The findings marked the second consecutive year of increased MDMA use among 10th- and 12th-graders and the first increase among 8th-graders. In 2000, 8.3 percent of 12th-graders reported that they had used MDMA at least once in the past year, up from 5.6 percent in 1999 and 3.6 percent in 1998. Eighth-graders' use of the drug increased from 1.7 percent in 1999 to 3.1 percent in 2000. Among 10th-graders, past-year MDMA use remained statistically unchanged, at 5.4 percent in 2000, but use in the past month increased from 1.8 percent in 1999 to 2.6 percent last year, according to the study's principal investigator, Dr. Lloyd Johnston of the University of Michigan in Ann Arbor.

Use of steroids during the year prior to the survey rose from 1.7 percent in 1999 to 2.2 percent in 2000 among 10th-graders but remained stable at 1.7 percent among 8th- and 12th-graders. Among teenage males, where most steroid use is concentrated, past-year use was reported by 2.2 percent of 8th-graders, 3.6 percent of 10th-graders, and 2.5 percent of 12th-graders, Dr. Johnston said at a December 2000 press conference announcing the most recent findings.



Graph on Steroid Trends in High School Children

Graph on Steroid Trends in High School Children

The Monitoring the Future study, conducted by the University of Michigan's Institute for Social Research and funded by NIDA, has tracked high school seniors' illicit drug use and attitudes toward drugs since 1975. Younger teens, in grades 8 and 10, were added to the survey in 1991. Data for the 2000 survey represent responses of more than 45,000 students in 435 schools across the Nation to questions about lifetime use, use during the past year, use during the past month, and daily use of various illicit drugs, alcohol, cigarettes, and smokeless tobacco.

"This survey provides crucial information on the real-world experience of young people with drugs, and the recent increases in MDMA use are a major concern," said NIDA Director Dr. Alan I. Leshner. "Ecstasy is not a 'fun' drug. It is neurotoxic—it severely damages brain cells and has consequences that include dehydration, hypertension, hyperthermia, and heart or kidney failure."

The number of 8th-graders having used an illicit drug during the past year has declined steadily from 22.1 percent in 1997 to 19.5 percent in 2000. Among 10th-

"This survey provides crucial information on the real-world experience of young people with drugs."

graders, use of an illicit drug was reported by 38.5 percent in 1997 and 36.4 percent in 2000. For seniors, past-year use of an illicit drug was reported by 42.4 percent in 1997 and by 40.9 percent in 2000.

Tenth-graders' past-month use of cigarettes was 23.9 percent in 2000, roughly the same as in 1999; however, daily cigarette smoking decreased significantly in this group, from 15.9 percent to 14.0 percent. Daily smoking among 12th-graders declined from 23.1 percent in 1999 to 20.6 percent in 2000.

Reductions in other measures of smoking also occurred among 8th-, 10th-, and 12th-graders. "For cigarettes, and for smokeless tobacco as well, the overall declines from peak levels of the mid-90s have been substantial," Dr. Johnston says. Alcohol use by teens remained largely unchanged in 2000.

For More Information

Additional information about the Monitoring the Future study can be obtained from NIDA Infofax at 1-888-NIH-NIDA (644-6432) or from NIDA's home page at www.drugabuse.gov. Information is also available from the Monitoring the Future home page at the Institute for Social Research at the University of Michigan: www.monitoringthefuture.org. Information about MDMA (ecstasy) is available at the NIDA club drugs Web site, www.clubdrugs.org. Information about steroids is available at NIDA's steroids Web site, www.steroidabuse.org. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

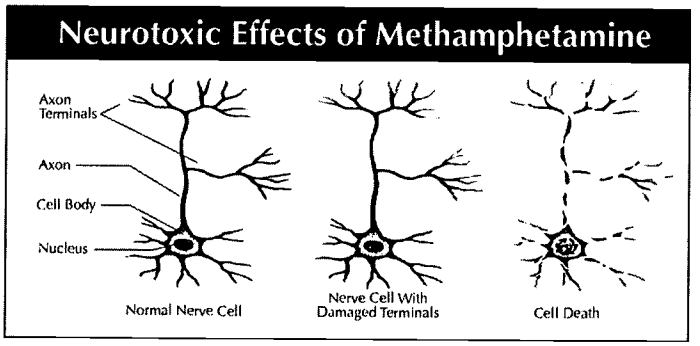
Research Findings

Volume 15, Number 4 (September, 2000)

Methamphetamine Brain Damage in Mice More Extensive Than Previously Thought

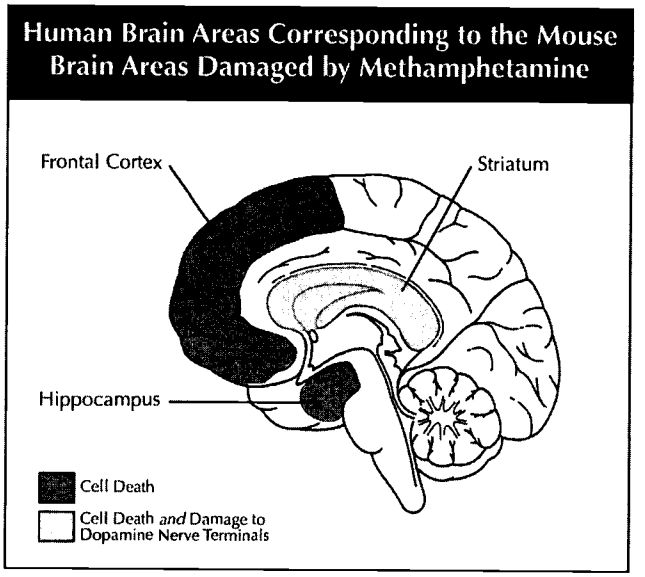
By Robert Mathias, *NIDA NOTES* Staff Writer

NIDA researchers have found that, when it comes to brain cells, "speed" actually does kill. "Speed" is a street name for methamphetamine, a powerfully addictive stimulant. Previous research had shown that methamphetamine damages but does not kill certain nerve cells in brain structures that control movement. The new research, conducted in mice, indicates that methamphetamine-induced damage prompts other nerve cells in brain regions involved in cognition as well as movement to self-destruct. The new findings raise concerns that methamphetamine may have significantly more harmful long-term consequences than previously thought, the researchers say.



Previous research showed that methamphetamine damages the nerve terminals of dopamine-producing brain cells. The new research shows methamphetamine also triggers a natural mechanism called apoptosis that prompts the complete disintegration and death of additional nerve cells in other brain regions.

Previous research showed that methamphetamine damages the nerve endings of brain cells containing dopamine, a chemical messenger that plays a role in movement and pleasure. Animal studies indicate that a gradual, partial recovery occurs in the dopamine system when methamphetamine exposure is stopped. For example, a recent imaging and postmortem study of the brains of monkeys found substantial recovery in dopamine function over an 18-month period following the animals' last e xposure to the drug. However, human brain imaging studies suggest that significant damage to nerve endings of dopamine-containing cells persists in the brains of chronic methamphetamine abusers for at least 3 years after they have stopped using the drug. The damage, which affects dopamine nerve endings located in the brain structures that make up the striatum, is similar to but less extensive than that caused by Parkinson's disease.



Methamphetamine-induced damage to nerve terminals of dopamine-producing cells occurs primarily in a brain region called the striatum. Methamphetamine-induced apoptosis killed off different types of nerve cells in the frontal cortex, the hippocampus, and the striatum in mice.

"People used to think that the most serious methamphetamine-induced damage was to dopamine nerve terminals because it put people at risk for developing Parkinson's disease as they got older," says Dr. Jean Lud Cadet, clinical director of NIDA's Intramural Research Program (IRP). "We've now shown in our lab that methamphetamine is much more toxic than previously thought. It does not just destroy the endings of dopamine-containing nerve cells, it also kills other nerve cells that produce other neurotransmitters in additional brain pathways," he says.

IRP researchers led by Dr. Cadet first linked this widespread loss of brain cells to a natural mechanism called apoptosis, through which the body programs unhealthy cells to kill themselves. In a study in cell cultures, they showed that treating rat brain cells with methamphetamine caused cell death marked by apoptotic patterns, such as DNA fragmentation and disintegration of cell bodies.

Subsequent studies in genetically engineered mice that lacked specific genes known to promote or suppress programmed cell death suggested that at least part of the nerve damage caused by methamphetamine may result from activation of the molecular machinery that is involved in apoptosis. The strongest evidence that methamphetamine unleashes widespread apoptosis in animals came in a recent study that showed the drug caused DNA fragmentation and loss of nerve cell bodies in the striatum, the hippocampus, and the frontal cortex of mice brains.

"Although these findings are in mice, if methamphetamine kills nerve cells in the same brain regions of humans who abuse the drug, the functional consequences could be significant," Dr. Cadet says. Loss of cells in the hippocampus and cortex could damage memory, cognitive function, and decision-making capacity, he says. Loss of striatal cells could lead to serious movement disorders that resemble tardive dyskinesia and Huntington's chorea.

Recent brain imaging studies in former methamphetamine abusers conducted by Dr. Richard Ernst and Dr. Linda Chang at the Harbor-UCLA Medical Center in Torrance, California, provide additional support for the finding that methamphetamine abuse causes brain cell death, says Dr. Cadet. The California researchers found alterations in brain chemistry in long-term methamphetamine abusers indicative of nerve cell loss or damage similar to that found in people suffering from strokes or Alzheimer's disease (see "Brain Imaging Studies Show Long-Term Damage From Methamphetamine Abuse").

If methamphetamine kills brain cells in humans, it may cause cognitive impairments that will have to be addressed when treating methamphetamine abusers, Dr. Cadet says. Although impaired people can do well in treatment, it is possible that developing medications to repair the brain could help such patients to do even better, he says. (See "NIDA Pursues Many Approaches to Reversing Methamphetamine's Neurotoxic Effects")

Sources

- Cadet, J.L.; Ordonez, S.V.; and Ordonez, J.V. Methamphetamine induces apoptosis in immortalized neural cells: Protection by the proto-oncogene, bcl-2. *Synapse* 25:176-184, 1997.
- Deng, X; Ladenheim,B.; Tsao, L.I.; and Cadet, J.L. Null mutation of c-fos exacerbation of methamphetamine-induced neurotoxicity. *Journal of Neuroscience* 19(22):10107-10115, 1999.
- Melega, W.P. Recovery from methamphetamine induced long-term nigrostriatal dopaminergic deficits without substantia nigra cell loss, Brain Research, in press.
- McCann, U.D.; Wong, D.F.; Yokoi, F.; Villemagne, V.; Dannals, R.F.; and Ricaurte, G.A. Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: Evidence from positron emission tomography studies with [11C]WIN-35,428. *Journal of Neuroscience* 18(20):8417-8422, 1998. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 4 (September, 2000)

NIDA Pursues Many Approaches to Reversing Methamphetamine's Neurotoxic Effects

By Robert Mathias, *NIDA NOTES* Staff Writer

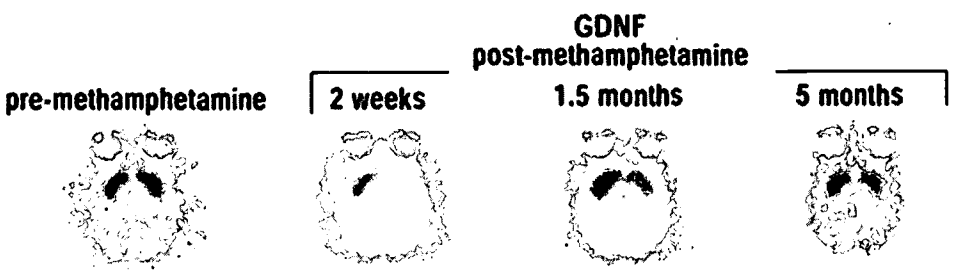
NIDA-supported scientists are pursuing a number of promising approaches to blocking or reversing some of the brain damage wreaked by chronic abuse of methamphetamine. Research has shown that methamphetamine can damage blood vessels and nerve endings in the brain and cause changes in brain chemicals. These effects put chronic methamphetamine abusers at risk for cognitive impairment and early onset of movement disorders associated with aging. (See "Methamphetamine Brain Damage in Mice More Extensive Than Previously Thought")

In January, NIDA's Division of Treatment Research and Development (DTR&D) convened a "Methamphetamine Addiction Treatment Think Tank." The meeting brought together preclinical and clinical researchers to set up a new program within NIDA's Medications Development Program to develop methamphetamine medications. The program now is selecting and setting up five sites to conduct clinical pharmacology and outpatient studies of medications proposed to treat different aspects of methamphetamine abuse, beginning with methamphetamine addiction. Overdose, neurodegeneration and cognitive impairment, psychoses, and movement disorders will be secondary targets.

"The first priority of the methamphetamine medications development program is to develop medications to treat methamphetamine addiction," says Dr. Ahmed Elkashef of DTR&D, who heads the program. Such medications are aimed at stopping or reducing methamphetamine abuse and not at directly reversing cognitive impairment or other clinical manifestations of methamphetamine's neurotoxic effects when they already have occurred in drug abuse treatment patients, Dr. Elkashef says. However, by reducing drug use, this approach could stop additional neurotoxic damage that might occur with continuing drug use, he says.

In addition to preventing new brain damage, addiction treatment medications may also help treat some of the clinical manifestations of methamphetamine neurotoxicity. "We will assess cognitively impaired patients to see if medications that stop or reduce methamphetamine abuse also improve cognitive functioning," Dr. Elkashef says. Program scientists also plan to test a long list of promising medications that may be able to reverse cognitive impairment caused by methamphetamine abuse, Dr. Elkashef says.

One of the first compounds the program will test—selegiline—is a medication that has the potential to treat both methamphetamine addiction and its associated cognitive impairment. NIDA has been testing selegiline, an approved treatment for some symptoms of Parkinson's disease, as a cocaine treatment medication. Selegiline's neuroprotective effects counter several possible mechanisms of methamphetamine neurotoxicity, Dr. Elkashef says. "This medication has been shown to reduce cognitive impairments among HIV-positive patients, and we expect it to help treat that aspect of methamphetamine abuse," he says.



These PET images show brain activity of a chemical messenger called dopamine (shown by dark color) in a monkey that was pretreated with glial-derived neurotrophic factor (GDNF) 1 week before being administered a neurotoxic dose of methamphetamine. Later images showed that the treated monkey had significantly greater recovery of dopamine function than an untreated monkey, at all time points following methamphetamine administration. (Brain images by Dr. William P. Melega.)

Methamphetamine may damage the brain in many ways, including impairment of blood flow, production of harmful free radicals, and killing of brain cells. Thus, the methamphetamine medications development program also is considering using medications that have the potential to improve cognitive function by countering these effects.

Potential cognitive enhancers, such as Hydergine, are thought to improve overall brain function by increasing blood flow and brain metabolism. Free radical scavengers, such as vitamin E, boost natural protective chemicals and processes that reduce brain damage caused by free radicals. Hydergine has shown modest success in improving alertness and short-term memory in stroke patients and individuals with Alzheimer's disease. Vitamin E administered with selegiline has slowed progression of Parkinson's disease and reduced severity of abnormal movements in tardive dyskinesia patients.

One possible strategy to address cognitive impairment in methamphetamine-addicted patients would be to add potential cognitive enhancers to drug addiction treatment medications, Dr. Elkashef says. However, the first step with each potential medication will be to assess whether clinical pharmacology interaction studies are needed to make sure it is safe to give it to outpatients who may continue to abuse methamphetamine, he stresses.

Developing Future Treatments

At a much earlier stage of treatment development, NIDA-supported researchers are conducting preclinical studies that could lead to the development of more sophisticated approaches to repairing methamphetamine-induced brain damage. Among the approaches that have shown promising results in animal studies are:

- DADLE ([D-Ala2,D-Leu5] enkephalin), a synthetic brain chemical and known tissue-protective agent. DADLE has been shown to block and reverse one type of methamphetamine-induced brain damage in mice;
- Neurotrophic factors, proteins produced by the body that nourish and maintain nerve cells. One of these factors, glial-derived neuro-trophic factor, has been shown to reduce methamphetamine's neurotoxic effects in monkeys;
- Genetic factors and natural anti-oxidants that promote cell survival. Boosting production of these genes and antioxidants in the brains of mice has been shown to prevent or moderate methamphetamine's neurotoxic effects.

Much additional research is needed to design safe and effective formulations of these treatments and ways to get them into the brain before researchers can begin testing in humans. However, these basic studies are increasing understanding of toxic reactions and protective mechanisms in the brain. This understanding should lead to the development of new medications that advance the goals of enabling patients to stop abusing methamphetamine and recover from at least some of the brain damage caused by the drug. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 3 (August, 2000)

Cocaine, Marijuana, and Heroin Abuse Up, Methamphetamine Abuse Down

By Robert Mathias, *NIDA NOTES* Staff Writer

Cocaine abuse indicators increased in many U.S. metropolitan areas during 1998 and the first half of 1999, according to a NIDA-supported network of drug abuse researchers who regularly report data on drug abuse in the United States. The rise follows several years of stable or declining use, the researchers reported at the December 1999 meeting of the Community Epidemiology Work Group (CEWG).

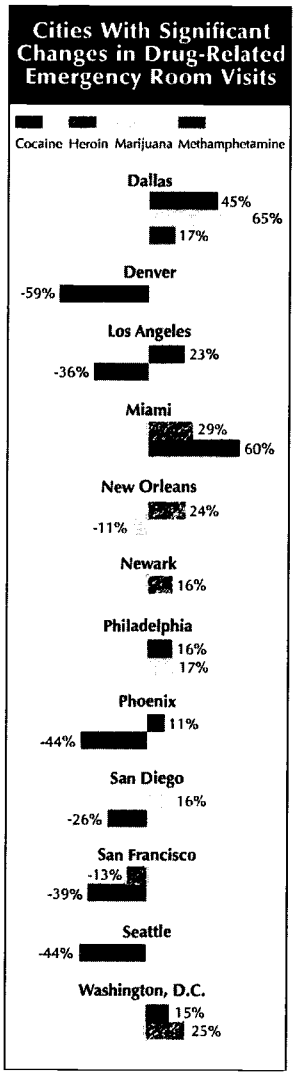
CEWG researchers meet twice a year to report on such drug abuse indicators as drug-related deaths, hospital emergency department (ED) visits, and treatment admissions. Data from 20 cities presented at the December meeting indicate that marijuana and heroin abuse also continued to increase in most areas of the country. However, methamphetamine abuse declined in most cities, including some areas that have been hardest hit by the problem. Highlights from the meeting's advance report are:

Cocaine. Indicators of cocaine abuse increased in half of the 20 CEWG cities, remained stable or mixed in 8, and decreased in 2. Five cities reported significant increases in cocaine-related ED incidents and 9 cities reported large increases in the number of cocaine-related deaths.

Heroin. Heroin abuse indicators increased in 10 CEWG cities, were stable or mixed in 9, and decreased in 1. Heroin abuse and snorting of the drug continued to increase among younger populations, such as college students. These trends were particularly apparent in East Coast cities where pure forms of white powder heroin, which can be snorted, are most available. Heroin-related deaths also increased in many areas of the country.

Marijuana. Seventeen CEWG cities reported increases in problems associated with marijuana abuse. The percentage of drug abusers whose primary drug of abuse was marijuana continued to increase in many cities. Rates of marijuana-related ED visits also continued the consistent, often dramatic, increases shown over the last 6 years. Increases in marijuana-related problems may be tied to increased availability, higher potency, and lower prices for the drug along with perceptions that marijuana abuse is less risky than abuse of other drugs, the report indicates.

Methamphetamine. Indicators of methamphetamine abuse decreased in West Coast and Southwest areas where abuse of the drug has been a major problem for years.



Many CEWG cities reported statistically significant increases from 1997 to 1998 in hospital emergency department (ED) visits due to cocaine, heroin, and marijuana use. However, methamphetamine-related ED visits declined sharply in most cities where rates had previously been highest. Source: Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, 1998 (July 1999 Update).

Sharp declines in methamphetamine-related ED visits were reported in 1998 in six CEWG areas. Several areas also reported that methamphetamine treatment admissions, hospital mentions, and deaths continued to decline in the first half of 1999. Researchers cited several possible reasons for these decreases, including initiation of national and community methamphetamine abuse prevention programs and enactment of laws that make it more difficult to obtain the chemicals needed to produce the drug.

Club Drugs. Thirteen cities reported problems with MDMA (ecstasy) abuse. The drug is available at raves and nightclubs in most areas. Ecstasy abuse also is increasing in other settings, such as college campuses. Nine areas reported GHB (gamma-hydroxybutyrate) abuse at raves and clubs. Numerous medical emergencies and several deaths were associated with GHB abuse.

For More Information

The CEWG "Advance Report, Epidemiologic Trends in Drug Abuse, December 1999," is available from NIDA's Web site, www.drugabuse.gov. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

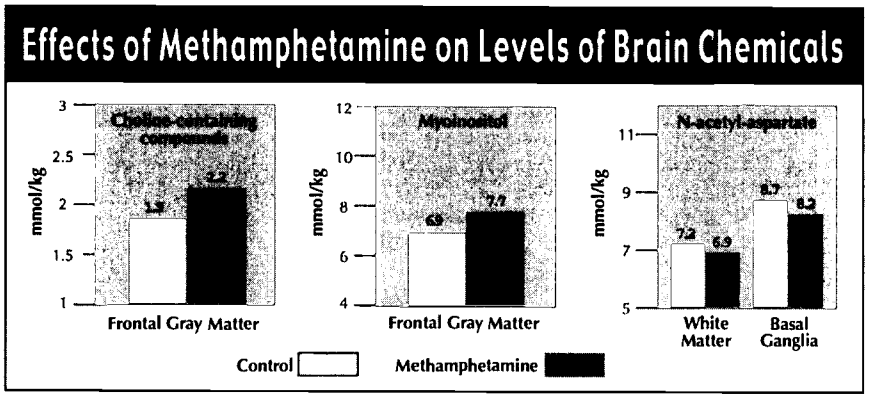
Research Findings

Volume 15, Number 3 (August, 2000)

Brain Imaging Studies Show Long-Term Damage From Methamphetamine Abuse

By Patrick Zickler, *NIDA NOTES* Staff Writer

Methamphetamine—commonly known as "speed," "meth," "ice," or "crystal"—is a powerfully addictive stimulant that acts on the central nervous system to produce increased wakefulness and physical activity as well as irritability, insomnia, confusion, tremors, convulsions, anxiety, paranoia, and aggressiveness. The drug increases heart rate and blood pressure and can irreversibly damage blood vessels in the brain. Now, NIDA-supported research has demonstrated that methamphetamine abusers risk long-term brain damage.



Neurons in three areas of the brain show changes in levels of brain chemicals that serve as indicators of health of brain cells. Levels of choline-containing compounds and myo-inositol are elevated and levels of N-acetyl-aspartate are reduced in methamphetamine abusers who have not used the drug for at least 2 weeks and up to 21 months. The changes in concentrations of these chemical markers suggest that methamphetamine use may result in long-term damage to brain cells used in thinking.

Dr. Thomas Ernst and Dr. Linda Chang at the Harbor-UCLA Medical Center in Torrance, California, used a noninvasive brain imaging technique called magnetic resonance spectroscopy (MRS) to measure levels of brain chemicals that indicate whether brain cells are healthy or are diseased or damaged. "We found abnormal brain chemistry in methamphetamine users in all the brain regions we studied. In one of the regions, the amount of damage was also related to the history of drug use-those abusers who had the greatest cumulative lifetime methamphetamine use had the strongest indications of cell damage," Dr. Chang says.

In each of the participants, the researchers examined a midfrontal region consisting largely of "gray matter"—nerve cell bodies and short extensions called dendrites that communicate with neighboring neurons—and an area in the basal ganglia, a neuron-dense region at the top of the brain stem. They also examined a right frontal area composed largely of "white matter," or long nerve cell extensions called axons that communicate with more distant regions of the brain. These brain regions were selected because they are areas of high activity of dopamine, a neurotransmitter involved in the "rush" and pleasure associated with addictive drugs.

The researchers measured levels of N-acetyl-aspartate (NAA), a metabolite produced only in neurons. "NAA levels are a measure of the viability and density of neurons," Dr. Ernst says. "Many diseases associated with brain cell loss or damage, such as Alzheimer's disease, stroke, and epilepsy, are also associated with reduced NAA."

The scientists also measured levels of two other chemical markers—choline-containing compounds and myo-inositol (MI)—associated mostly with specialized cells called glial cells. "The primary role of glial cells is to maintain normal function of neurons, including repair of injury to the cells. Increases in glial markers suggest proliferation of these support cells in response to neuronal damage," Dr. Ernst explains.

Dr. Chang and Dr. Ernst measured levels of the chemical markers in 26 participants who had a history of methamphetamine abuse but had not used the drug for periods ranging from 2 weeks to 21 months with a median of 4.25 months since last use. They compared the results to measurements of 24 participants who had no history of methamphetamine use.

Among the methamphetamine abusers, NAA levels were reduced by 5 percent in the frontal white matter and 6 percent in the basal ganglia compared with levels among nonusers. "The reduced concentrations of NAA in the drug users' brains suggest that long-term methamphetamine abuse results in loss of or damage to neurons," Dr. Ernst says. Methamphetamine abusers also showed

increases of 11 percent in levels of MI and 13 percent in levels of choline-containing compounds in the frontal gray matter compared with nonusers. "This suggests an increased number or size of glial cells as a reaction to the injurious effects of the drug," he adds.

"Methamphetamine may be substantially toxic to the cells we use in thinking," Dr. Ernst says. "This long-term, and perhaps permanent, alteration in basic brain chemistry is additional evidence that methamphetamine abuse, like abuse of other drugs, should be considered a brain disease and treated accordingly."

Sources

- Ernst, T.; Chang, L.; Leonido-Lee, M.; and Speck, O. Evidence for long-term neurotoxicity associated with methamphetamine abuse: a 1H MRS study. *Neurology* 54(6):1344-1349, 2000. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 2 (August, 2000)

Ketamine, PCP, and Alcohol Trigger Widespread Cell Death In the Brains of Developing Rats

By Robert Mathias, *NIDA NOTES* Staff Writer

NIDA-supported study has shown that prenatal exposure to drugs such as phencyclidine (PCP), ketamine, and alcohol causes widespread damage to the developing rat brain. Though conducted with animals, the study raises concerns not only about the effects of abusing these drugs during pregnancy but also about the legitimate use of ketamine and similar anesthetic medications during pregnancy and early childhood, the researchers say.

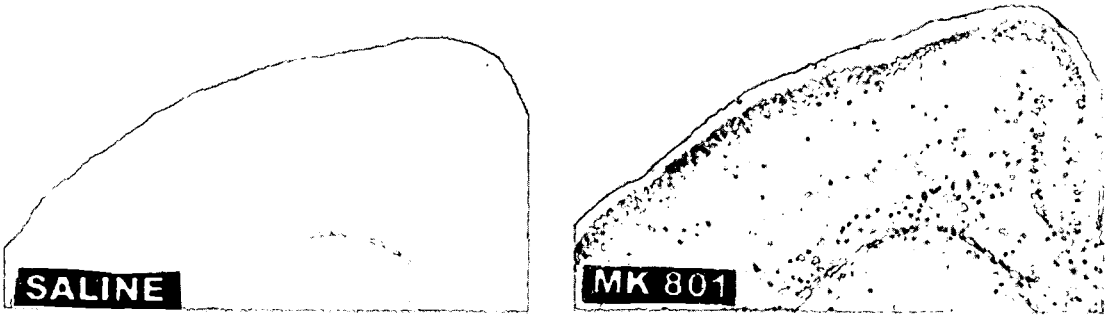
PCP, ketamine, and alcohol all belong to a class of drugs that prevent brain cells from picking up glutamate, a chemical messenger that cells use to communicate with each other. The new research by Dr. John Olney of Washington University School of Medicine in St. Louis and scientists from Humboldt University in Berlin and University College in London found that when such drugs block developing nerve cells in late fetal and newborn rats from receiving glutamate, they dramatically accelerate a natural process called programmed cell death.

Normally, programmed cell death, or apoptosis, serves a positive function. During development of the central nervous system, this process eliminates brain cells that are not serving any useful purpose. Such cells are abundant when the developing brain is rapidly generating billions of new cells and connecting them with each other. Cells needed only during early stages of development, surplus cells, and faulty cells that fail to complete their proper connections all must be eliminated to ensure efficient brain functioning.

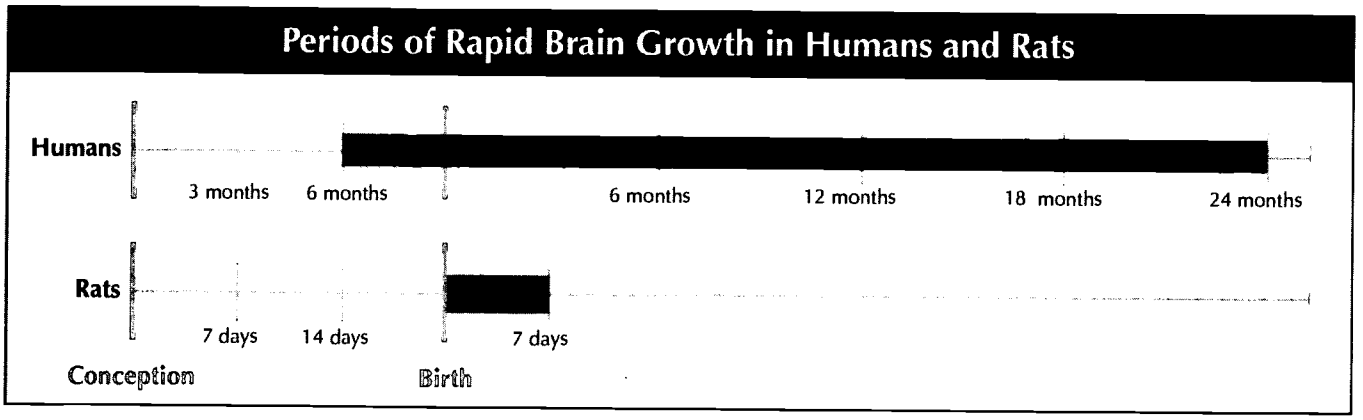
However, in Dr. Olney's study, the researchers found that a single administration of a drug that blocked glutamate transmission for at least 4 hours when rats' brains were undergoing rapid development triggered a massive wave of programmed cell death, eradicating millions of nerve cells in key areas of the brain.

In the study, the researchers administered a drug called MK801 to pregnant and newborn rats. Like PCP, ketamine, and alcohol, MK801 blocks N-methyl-D-aspartate (NMDA) receptors, sites on nerve cells through which glutamate transmits its signals. The scientists administered the substance to pregnant rats 72, 48, or 24 hours before the rats gave birth and to infant rats on the 1st, 3rd, 7th, 14th, or 21st day of life. Examination of the fetal and infant brains 24 hours after treatment showed MK801-treated rats had very high concentrations of degenerating nerve cells in many brain regions. Rats treated with inactive saline solution on the same days had low concentrations of degenerating cells, consistent with natural programmed cell death.

MK801 triggered the most extensive programmed cell death in the forebrain of rats treated when they were 7 days old, a period when this important brain area is developing rapidly. "Many areas of the brain were particularly hard-hit," says Dr. Olney. For example, the numbers of degenerating neurons in treated rats were 3- to 39-fold higher than the numbers in untreated rats in several areas of the thalamus and cerebral cortex. "These regions of the brain are central to how [animals, including humans,] interact with the environment, integrate sensory information into the brain, and perform cognitive processes," Dr. Olney says.



NMDA-receptor blocking drugs, such as PCP, ethanol, and MK801, triggered extensive programmed cell death in the forebrains of 7-day-old rats. These brain images were obtained 24 hours after rats were treated with either MK801 or an inactive saline solution. The dark spots in the brain of the MK801-treated rat show millions of degenerating nerve cells in key brain areas compared to the insignificant amounts of degenerating nerve cells in the brain of the saline-treated rat. (Brain images at X9.8 magnification.)



Rats are born at an earlier stage of their development than humans. The rapid brain growth that occurs in their first week of life corresponds to the growth spurt in human brains that begins in the last trimester of pregnancy and continues in the first few years of life. Because NMDA-receptor blocking drugs triggered the most damage to the rats' brains during this period, the researchers at Washington University speculate that the human brain may be most vulnerable to such drugs during the entire third trimester and approximately the first 2 years of life.

Because rats are born at an earlier stage of their development than humans, the rapid brain growth that occurs in their first week of life corresponds to the growth spurt in human brains that begins in the last trimester of pregnancy and extends through the first 2 to 3 years of life. This indicates that the period of peak vulnerability of the human forebrain to the nerve damage induced by NMDA-receptor blocking drugs may include the entire third trimester, the researchers conclude. It also indicates a need to re-evaluate the use of NMDA-receptor blocking anesthetic medications, such as ketamine and nitrous oxide, during pregnancy and early childhood. "Additional research is needed to determine if we can establish a margin of safety for using these agents," Dr. Olney says.

To confirm that it was the blockade of NMDA receptors that induced the damaging effects in the developing rat brain, the researchers administered several other NMDA-receptor blocking drugs, including PCP and ketamine, to newborn rats. These drugs all triggered a pattern of cell degeneration similar to that induced by MK801. However, several factors may limit the amount of fetal brain damage that could occur when women abuse these drugs during pregnancy, Dr. Olney notes. For example, ketamine is a relatively short-acting drug, and the study used several doses to ensure sufficient receptor blockade to trigger apoptosis. As for PCP, its ability to induce psychotic effects in humans reduces the likelihood of someone taking multiple doses. "Nevertheless, the duration of blockade of the NMDA receptor that occurs when people abuse these drugs would probably be right at the threshold where prenatal damage could result," he says, "although such damage would probably not be as severe as shown in this study."

"These findings suggest that pregnant women who abuse drugs such as ketamine and PCP are risking considerable harm to the brains of their unborn children during critical stages of their development," says Dr. Jerry Frankenheim of NIDA's Division of Neuroscience and Behavioral Research. If the damage to nerve cells caused by these drugs in rats occurs in the human fetus, it could lead to learning and behavior problems in childhood, he says.

The developmental harm that could result from fetal brain damage caused by using NMDA-receptor blocking drugs during pregnancy can be illustrated by the known effects of using alcohol during pregnancy, says Dr. Olney. These effects, which are referred to as fetal alcohol syndrome, can range from attention-deficit hyperactivity disorder and various degrees of learning disabilities to mental retardation.

NMDA-blockade is one of the primary ways that alcohol damages the developing brain, according to a separate study conducted by Dr. Olney and his colleagues. They found that blocking NMDA receptors with alcohol for several hours during periods when the developing brain is most vulnerable produces damage similar to that caused by MK801 and PCP. "The kind of damage to these brain centers that we are finding with drugs such as alcohol, PCP, and ketamine can have far-reaching effects on behavioral and psychiatric well-being," he says.

Sources

- Ikonomidou, C.; Bosch, F.; Miksa, M.; Bittigau, P.; Vöckler, J.; Dikranian, K.; Tenkova, T.I.; Stefovska, V.; Turski, L.; and Olney, J.W. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science* 283(5398):70-74, 1999. [Abstract]
- Ikonomidou, C.; Bittigau, P.; Ishimaru, M.J.; Wozniak, D.F.; Koch, C.; Genz, K.; Price, M.T.; Stefovska, V.; Hörster, F.; Tenkova, T.; Dikranian, K.; and Olney, J.W. Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. *Science* 287(5455): 1056-1060, 2000. NN

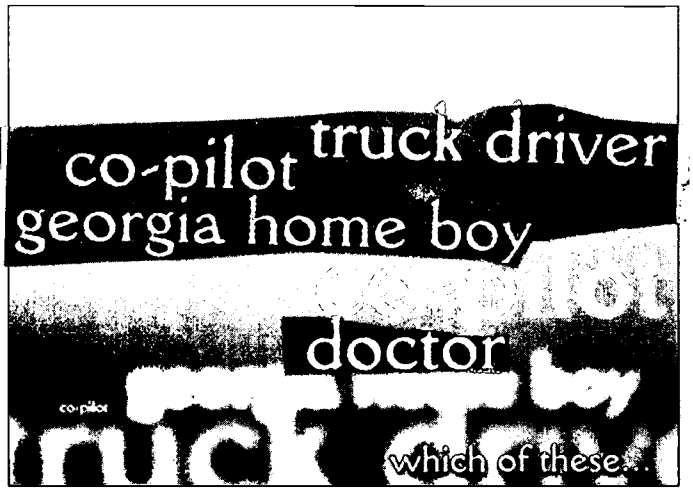
NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 2 (August, 2000)

NIDA Research Informs Lawmakers on GHB Risks

NIDA research provided important scientific background for the development of a law to control GHB (gammahydroxybutyrate), a club drug that is used at dance clubs and has reportedly been used to facilitate sexual assault. In March 1999 testimony before the House Committee on Commerce Subcommittee on Oversight and Investigations, Dr. Stephen Zukin, associate director of NIDA's Division of Treatment Research and Development, described the drugs' actions on the brain and reported recent data from NIDA's Community Epidemiology Work Group that reported increasing use of the drugs. The bill increases criminal penalties for illicit manufacture, possession, and distribution of GHB. It also makes the drug's precursor chemicals susceptible to increased regulation. President Clinton signed the bill into law (P.L. 106-172) on February 18, 2000. NN



NIDA's congressional testimony is one part of its efforts to increase awareness of the dangers of club drugs. More than 300,000 "Hot Stamp" cards like the one at right have been placed in restaurants, bars, coffeeshops, and bookstores.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

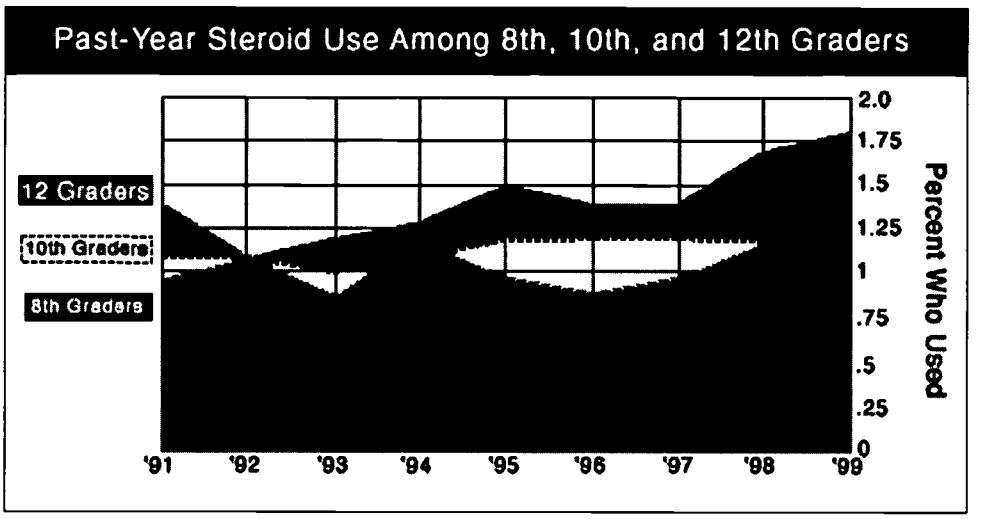
Research Findings

Volume 15, Number 1 (March, 2000)

Overall Teen Drug Use Stays Level, Use of MDMA and Steroids Increases

By Steven Stocker, *NIDA NOTES* Contributing Writer

Drug use among the Nation's adolescents generally held steady in 1999 with the exception of MDMA, or "ecstasy," and steroids, according to the most recent Monitoring the Future study. This annual study, supported by NIDA and conducted by the Institute for Social Research at the University of Michigan in Ann Arbor, surveys drug use among 8th-, 10th- and 12th-graders in the United States.



Secretary of Health and Human Services Dr. Donna E. Shalala presented the results of the study at a press conference in Washington, D.C., in December. She noted that for the third year in a row adolescent drug use rates stayed the same or declined after the rapid rise in the early 1990s. "Today's report confirms what we've suspected for some time: that the trend of increased drug use among America's young people is grinding to a halt," she said. Also participating in the press conference were White House Drug Policy Director General Barry McCaffrey, NIDA Director Dr. Alan I. Leshner, and principal investigator Dr. Lloyd Johnston of the University of Michigan.

Although no significant changes occurred in 1999 in the use of marijuana, amphetamines, hallucinogens, tranquilizers, or heroin, several significant changes in other drug use did occur, including:

- a reduction in the use of crack cocaine by 8th- and 10th-graders, following several years of gradually increasing use;
- a reduction in the use of crystal methamphetamine, or "ice," among 12th-graders, reaching the lowest level in 5 years;
- a reduction in cigarette smoking among 8th-graders;
- an increase in the use of MDMA among 10th- and 12th-graders; and
- an increase in the use of anabolic steroids among 8th- and 10th- graders, primarily among boys.

Anabolic steroids are synthetic derivatives of the male hormone testosterone that promote skeletal muscle growth. They have legitimate medical uses but sometimes are used illegally to enhance athletic performance and improve physical appearance. Side effects can include liver tumors, high blood pressure, wild mood swings, and violent behavior.

Referring to the increase in MDMA use, Dr. Johnston said that the forces that help spread the use of a new drug by adolescents generally work more quickly than the forces that help to contain its use. "When a newer drug comes onto the scene, young people hear much more about its supposed benefits than about its potential harms," he said. "It can take some time for evidence of the adverse consequences to become known to them." General McCaffrey noted that many adolescents imagine that MDMA is a relatively safe drug, but recent NIDA-funded studies show that it may cause long-term brain damage.

MDMA is one of several drugs that are known collectively as "club drugs" because they are used at dance clubs and all-night dance parties called "raves." Other club drugs include LSD, GHB, Rohypnol, methamphetamine, and ketamine. NIDA recently announced an increase of 40 percent in its funding for research on club drugs. It has also joined with other national organizations on a multimedia campaign to educate the public about the dangers of using these drugs.

For More Information

Additional information about the Monitoring the Future study can be obtained from NIDA Infofax at 1-888-NIH-NIDA (644-6432) or from NIDA's home page at www.drugabuse.gov. (Click on Information on Drugs of Abuse.) Information is also available from the Monitoring the Future home page at the Institute for Social Research at the University of Michigan at www.monitoringthefuture.org. Information about club drugs can be found at the NIDA Club Drugs Web site: www.clubdrugs.org. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 14, Number 6 (March, 2000)

NIDA Launches Initiative to Combat Club Drugs

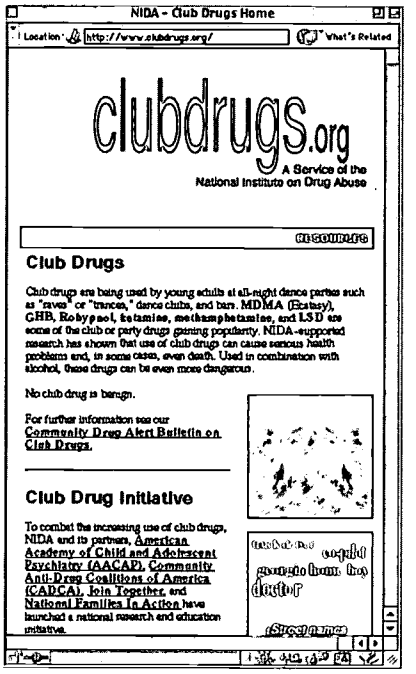
By Patrick Zickler, *NIDA NOTES* Staff Writer

Responding to the alarming recent rise in use of club drugs, NIDA has initiated a broad-based public initiative to inform and educate teens, young adults, parents, and communities about the dangers of drugs such as "ecstasy," "roofies," and GHB.

"Young adults believe club drugs can harmlessly enhance their experience at dance parties and 'raves,' but there is no safe way to use any of these drugs," said NIDA Director Dr. Alan I. Leshner. "Research shows that some of the so-called club drugs have long-lasting effects on the brain. Combined with alcohol, these drugs are even more dangerous, sometimes deadly. There is no such thing as a harmless club drug. There is no such thing as recreational drug use."

At a Washington, D.C., press conference, Dr. Leshner announced that NIDA was teaming up with the American Academy of Child and Adolescent Psychiatry, the Community Anti-Drug Coalitions of America, Join Together, and National Families in Action to increase public awareness of the effects of club drugs. As part of the initiative, Dr. Leshner said, NIDA is increasing its funding for club drug research by 40 percent, to $54 million. In addition, NIDA has developed a multimedia campaign, including a new Web site—www.clubdrugs.org—to disseminate science-based information about the drugs.

"Accurate, credible information is the most powerful weapon we have to combat the increasing use of these dangerous drugs," said NIDA Associate Director Dr. Timothy P. Condon. "Our Web site will provide up-to-date information 24 hours a day. We are distributing 250,000 copies of a special Community Drug Alert Bulletin that explains where these drugs are being used and what science has revealed about the way they work. And we are placing more than 330,000 free colorful 'HotStamp' cards—which show how using ecstasy can disrupt brain function—in restaurants, bars, coffee shops, and bookstores."



This new Web site—www.clubdrugs.org—provides information on club drugs and their effects.

NIDA's initiative represents an important first step in reducing club drug use, said Dr. David Rosenbloom, director of Join Together, a project organized by the Boston University School of Public Health to serve as a national resource for information that community-level organizations can use to prevent drug use. "This is NIDA's early warning alarm. It sends a very clear signal to the Nation," Dr. Rosenbloom said. "We need to act quickly, distribute accurate scientific information, and reverse the pattern of increasing use of these dangerous drugs." NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 6 (March, 2000)

A Club Drug Alert

NIDA Director Dr. Alan I. Leshner

For several years, NIDA monitoring systems have registered a nationwide pattern of drug use centered on all-night party and "rave" dance clubs and bars. The drugs reported in these scenes are extremely diverse and vary among locales. Overall, they include drugs that have long been abused, such as marijuana and cocaine, and drugs whose abuse is a more recent development, such as methamphetamine, ecstasy, gamma-hydroxybutyrate (GHB), flunitrazepam (Rohypnol), and ketamine. Some are stimulants, some depressants, and some hallucinogens. Some are prescription drugs that are made in licensed factories using strict quality control, but illegally diverted for abuse. Others have no legitimate medical uses and are produced clandestinely.

Because these drugs are relatively new, some vulnerable individuals may imagine that taking them is safe.

Because of this diversity, "club drugs" is an ambiguous and flexible term. However, it clearly applies to methamphetamine, ecstasy, GHB, and Rohypnol, which have become widespread in the 1990s in tandem with contemporary club culture.

The novelty of many club drugs is undoubtedly one reason for the recent surge in their use. Because these drugs are relatively new, some vulnerable individuals may imagine that taking them is safe—that their reported adverse effects are rare or exaggerated, and that such reactions could never affect them personally. In contrast, few can harbor such misperceptions about older drugs. Cocaine, for example, was widely used in dance clubs and elsewhere in the 1980s, but its use has receded as its health and social costs have become well known.

Scientists still have much to learn about club drugs. However, they have already shown that these substances can cause serious and perhaps permanent impairments and sometimes death.

Methamphetamine (also known as "speed" and "crank") is a more powerful variation of a stimulant found in some diet medications. The well-documented effects of long-term methamphetamine exposure include anxiety, confusion, paranoia, hallucinations, and cardiovascular problems. This drug is highly addictive. Last year in San Diego and Seattle, more people came to publicly funded treatment programs for help getting off methamphetamine than for help getting off any other drug.

NIDA-supported researchers using new brain imaging techniques have produced vivid and worrisome evidence of methamphetamine's ill effects. The pictures show that the drug damages brain cells that produce the neurotransmitters dopamine and serotonin. These neurotransmitters contribute to pleasure, motivation, cognition, and memory. Their loss may underlie a syndrome of slowed thinking, depressed mood, and motor impairment that has occurred in some heavy users of methamphetamine. Methamphetamine abuse also facilitates the spread of HIV/AIDS through unsafe sex and shared injection equipment.

Ecstasy (also called "X," "Adam," and "MDMA") is both a stimulant and a hallucinogen. Rave-goers use it for energy to keep on dancing and for mood enhancement. Ecstasy increases the heart rate and body temperature and has occasionally contributed to heart and kidney failure. The drug also appears to mask the sense of thirst—a potentially hazardous effect if one is dancing for hours on end in a crowded, sweltering club. Ecstasy users have died from acute dehydration.

Ecstasy also appears to have long-term effects. In a recent study, long-term ecstasy users had residual problems of verbal and visual memory 2 weeks after stopping the drug. Brain imaging studies have shown that the drug damages brain cells that produce serotonin. We still do not know if these cells regenerate, so the memory loss—and perhaps additional still-to-be-discovered serotonin-related impairments—may be long-lasting or permanent. In addition, a study in Great Britain documented an elevated incidence of congenital abnormalities in the children of women who took ecstasy during pregnancy.

GHB (sometimes called "G" or "liquid ecstasy") and Rohypnol (known as "roofie" or "Roche") have become notorious for their use in crimes, particularly rape.

Colorless, odorless, and tasteless, they can be slipped into drinks and ingested without the victim having any clue. They cause sedation, often rendering the victim helpless. They also produce amnesia, making it very difficult to arrest and convict a perpetrator.

GHB is also dangerous when taken knowingly for its relaxing effects. Because GHB is illegal and made by amateurs, samples vary many-fold in their strength and purity. Users simply cannot know how much they are getting. Overdoses are common, with consequences of coma and sometimes death from respiratory arrest. As of mid-1998, GHB has been implicated in at least 26 deaths.

Because widespread use of ecstasy, GHB, and Rohypnol is relatively recent, the worst effects of these drugs may be the ones that are not yet known. For example, the full addictive potential of these substances has not yet been determined. There are indications, however, that the potential may be significant. GHB users have reported that they need higher and higher doses to get the effects that they want, and that when they try to quit, they can't.

An additional challenge to scientists—and peril to users—is the fact that club drugs are often taken in combination or with other intoxicants. GBH, for example, is frequently consumed with alcohol, which is also a depressant. A significant percentage of those who have died with GHB have also had alcohol in their blood. In Seattle and Miami, ecstasy is sometimes taken mixed with LSD, psilocybin, or heroin. It is very likely that such combinations will affect the body and brain in ways that are more deleterious than either drug alone.

In December, NIDA launched a major initiative to warn the Nation not to underestimate the harm that club drugs do (see "NIDA Launches Initiative to Combat Club Drugs," p.1). What is at stake is the potential for a new national drug tragedy just when we seem to be emerging from the worst devastation of the crack cocaine epidemic.

NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 14, Number 6 (March, 2000)

What Are Club Drugs?

MDMA: methylenedioxymethamphetamine—Ecstasy, X, XTC, Adam

A stimulant similar to methamphetamine, MDMA is usually taken orally as a tablet. It causes increased heart rate and blood pressure, and may lead to an elevation of body temperature that causes kidney and cardiovascular failure. When combined with alcohol, MDMA can be extremely dangerous, sometimes fatal. Chronic abuse of MDMA may produce long-lasting neurotoxic effects in the brain.

GHB: gamma-hydroxybutyrate-Liquid Ecstasy, Georgia Home Boy, G

A clear odorless liquid, GHB is a central nervous system depressant and has been associated with poisonings, overdoses, and date rape. GHB overdose can lead rapidly to loss of consciousness, coma, and death. The purity and strength of individual doses of the drug can vary greatly, making overdoses likely.

Ketamine-K, Special K, Vitamin K, Cat Valium

Ketamine is a veterinary anesthetic that produces dissociative dream-like or hallucinatory effects. The drug is used as a liquid applied to marijuana or tobacco products or as a white powder that is snorted like cocaine. At high doses, ketamine produces delirium, amnesia, impaired motor function, and sometimes-fatal respiratory effects.

Rohypnol: flunitrazepam—Roofies, Rophie, Roche, Forget-me

A benzodiazepine sedative similar to Valium and Xanax, flunitrazepam is not approved for prescription use in the United States. The drug is taken orally in tablet form or dissolved in beverages. Because the drug is odorless and tasteless and produces amnesia, it can be administered to a person without his or her knowledge and has been associated with date rape and other sexual assaults.

Methamphetamine—Meth, Speed, Ice, Glass, Crystal, Crank

Methamphetamine, an odorless white crystalline powder, is a highly addictive stimulant that can be snorted, smoked, injected, or taken orally. The drug produces increased levels of activity, excited speech, and decreased appetite. Methamphetamine is a neurotoxin associated with long-lasting effects on the dopamine transporter system as well as with other dangerous health effects including aggression, violence, memory loss, psychotic behavior, and cardiac damage.

Lysergic Acid Diethylamide: LSD—Acid, Blotter, Cubes, Dots, L, Sugar

LSD is a powerful hallucinogen that is taken orally, usually on squares of blotter paper, sugar cubes, or pills that have absorbed the liquid drug. The drug produces profound abnormalities in sensory perception, including distortions of sound and sight, and emotional effects that create rapid mood swings ranging from intense fear to euphoria. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 14, Number 4 (November, 1999)

"Ecstasy" Damages the Brain and Impairs Memory in Humans

By Robert Mathias, *NIDA NOTES* Staff Writer

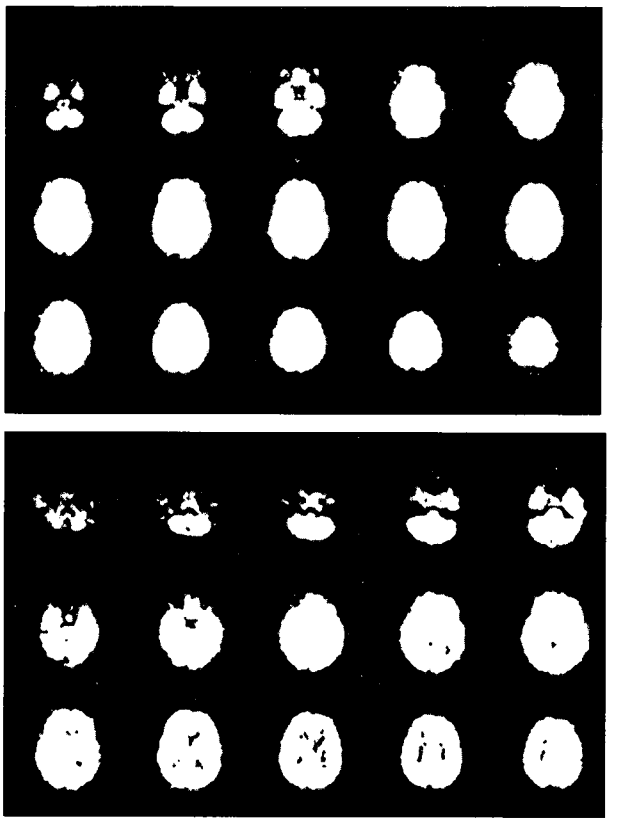
A NIDA-supported study has provided the first direct evidence that chronic use of MDMA, popularly known as "ecstasy," causes brain damage in people. Using advanced brain imaging techniques, the study found that MDMA harms neurons that release serotonin, a brain chemical thought to play an important role in regulating memory and other functions. In a related study, researchers found that heavy MDMA users have memory problems that persist for at least 2 weeks after they have stopped using the drug. Both studies suggest that the extent of damage is directly correlated with the amount of MDMA use.

"The message from these studies is that MDMA does change the brain and it looks like there are functional consequences to these changes," says Dr. Joseph Frascella of NIDA's Division of Treatment Research and Development. That message is particularly significant for young people who participate in large, all-night dance parties known as "raves," which are popular in many cities around the Nation. NIDA's epidemiologic studies indicate that MDMA (3,4-methylenedioxymethamphetamine) use has escalated in recent years among college students and young adults who attend these social gatherings.

In the brain imaging study, researchers used positron emission tomography (PET) to take brain scans of 14 MDMA users who had not used any psychoactive drug, including MDMA, for at least 3 weeks. Brain images also were taken of 15 people who had never used MDMA. Both groups were similar in age and level of education and had comparable numbers of men and women.

In people who had used MDMA, the PET images showed significant reductions in the number of serotonin transporters, the sites on neuron surfaces that reabsorb serotonin from the space between cells after it has completed its work. The lasting reduction of serotonin transporters occurred throughout the brain, and people who had used MDMA more often lost more serotonin transporters than those who had used the drug less.

Previous PET studies with baboons also produced images indicating MDMA had induced long-term reductions in the number of serotonin transporters. Examinations of brain tissue from the animals provided further confirmation that the decrease in serotonin transporters seen in the PET images corresponded to actual loss of serotonin nerve endings containing transporters in the baboons' brains.



These brain scans show the amount of serotonin activity over a 40-minute period in a non-MDMA user (top) and an MDMA user (bottom). Dark areas in the MDMA user's brain show damage due to chronic MDMA use.

"Based on what we found with our animal studies, we maintain that the changes revealed by PET imaging are probably related to damage of serotonin nerve endings in humans who had used MDMA," says Dr. George Ricaurte of The Johns Hopkins Medical Institutions in Baltimore. Dr. Ricaurte is the principal investigator for both studies, which are part of a clinical research project that is assessing the long-term effects of MDMA.

"The real question in all imaging studies is what these changes mean when it comes to functional consequences," says NIDA's Dr. Frascella. To help answer that question, a team of researchers, which included scientists from Johns Hopkins and the National Institute of Mental Health who had worked on the imaging study, attempted to assess the effects of chronic MDMA use on memory. In this study, researchers administered several standardized memory tests

to 24 MDMA users who had not used the drug for at least 2 weeks and 24 people who had never used the drug. Both groups were matched for age, gender, education, and vocabulary scores.

The study found that, compared to the nonusers, heavy MDMA users had significant impairments in visual and verbal memory. As had been found in the brain imaging study, MDMA's harmful effects were dose-relatedÑthe more MDMA people used, the greater difficulty they had in recalling what they had seen and heard during testing.

The memory impairments found in MDMA users are among the first functional consequences of MDMA-induced damage of serotonin neurons to emerge. Recent studies conducted in the United Kingdom also have reported memory problems in MDMA users assessed within a few days of their last drug use. "Our study extends the MDMA-induced memory impairment to at least 2 weeks since last drug use and thus shows that MDMA's effects on memory cannot be attributed to withdrawal or residual drug effects," says Dr. Karen Bolla of Johns Hopkins, who helped conduct the study.

The Johns Hopkins/NIMH researchers also were able to link poorer memory performance by MDMA users to loss of brain serotonin function by measuring the levels of a serotonin metabolite in study participants' spinal fluid. These measurements showed that MDMA users had lower levels of the metabolite than people who had not used the drug; that the more MDMA they reported using, the lower the level of the metabolite; and that the people with the lowest levels of the metabolite had the poorest memory performance. Taken together, these findings support the conclusion that MDMA-induced brain serotonin neurotoxicity may account for the persistent memory impairment found in MDMA users, Dr. Bolla says.

Research on the functional consequences of MDMA-induced damage of serotonin-producing neurons in humans is at an early stage, and the scientists who conducted the studies cannot say definitively that the harm to brain serotonin neurons shown in the imaging study accounts for the memory impairments found among chronic users of the drug. However, "that's the concern, and it's certainly the most obvious basis for the memory problems that some MDMA users have developed," Dr. Ricaurte says.

Findings from another Johns Hopkins/NIMH study now suggest that MDMA use may lead to impairments in other cognitive functions besides memory, such as the ability to reason verbally or sustain attention. Researchers are continuing to examine the effects of chronic MDMA use on memory and other functions in which serotonin has been implicated, such as mood, impulse control, and sleep cycles. How long MDMA-induced brain damage persists and the long-term consequences of that damage are other questions researchers are trying to answer. Animal studies, which first documented the neurotoxic effects of the drug, suggest that the loss of serotonin neurons in humans may last for many years and possibly be permanent. "We now know that brain damage is still present in monkeys 7 years after discontinuing the drug," Dr. Ricaurte says. "We don't know just yet if we're dealing with such a long-lasting effect in people."

Sources

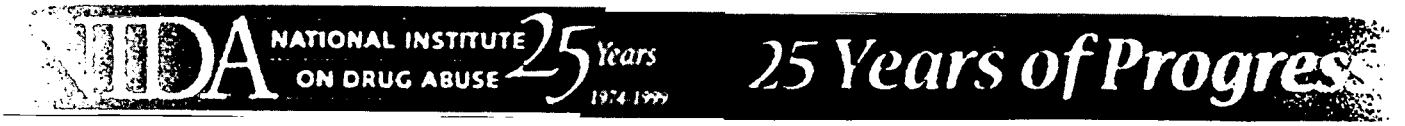
- Bolla, K.I.; McCann, U.D.; and Ricaurte, G.A. Memory impairment in abstinent MDMA ("ecstasy") users. *Neurology* 51:1532-1537, 1998.
- Hatzidimitriou, G.; McCann, U.D.; and Ricuarte, G.A. Altered serotonin innervation patterns in the forebrain of monkeys treated with MDMA seven years previously: Factors influencing abnormal recovery. *Journal of Neuroscience* 191(12):5096-5107, 1999.
- McCann, U.D.; Mertl, M.; Eligulashvili, V.; and Ricaurte, G.A. Cognitive performance in (±) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. *Psychopharmacology* 143:417-425, 1999.
- McCann, U.D.; Szabo, Z.; Scheffel, U.; Dannals, R.F.; and Ricaurte, G.A. Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 4 (November, 1999)

Targeting Methamphetamine Abuse



While the popularity of methamphetamine, a powerful and highly addictive stimulant, has waxed and waned over the years, NIDA-supported scientific research has continued to serve as the basis for the Nation's response to methamphetamine abuse and addiction.

NIDA's Community Epidemiology Work Group has tracked the patterns of methamphetamine manufacture and abuse throughout the U.S. Once seen primarily on the West Coast, methamphetamine has recently spread to urban and rural areas in the Midwest and certain areas in the Northeast.

Basic research supported by NIDA has examined how methamphetamine and similar drugs, such as ecstasy (MDMA), work in the brain and precisely how they damage brain cells. Researchers have also looked at the similarities and differences between methamphetamine and cocaine, as well as the relationship between methamphetamine abuse and the transmission of HIV/AIDS.

Other NIDA-supported research has sought to identify effective methods to treat methamphetamine addiction. At present, there is no medication to treat methamphetamine overdose or addiction. However, cognitive-behavioral interventions that help modify a patient's thinking and teach skills to cope with stressful situations have been effective in many cases.

"NIDA-supported research has examined how methamphetamine and similar drugs, such as ecstasy (MDMA), work in the brain."

Drug abuse prevention programs have not always addressed issues affecting drug use by high school and college students. However, NIDA-supported researchers have evaluated drug abuse prevention programs, which typically target elementary and intermediate school students, to determine their potential for reducing methamphetamine abuse in older adolescents who may have tried methamphetamine but are not yet addicted.

Most recently, NIDA has worked in partnership with its constituent professional organizations across the country to address the issue of methamphetamine abuse through its Town Meetings and the widespread distribution of a Community Drug Alert Bulletin on Methamphetamine. A methamphetamine component for NIDA's Mind Over Matter series for middle school students is currently under development. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 4 (November, 1999)

Facts About MDMA (Ecstasy)

MDMA (3,4-methylenedioxymethamphetamine) has a chemical structure similar to the stimulant methamphetamine and the hallucinogen mescaline and can produce both stimulant and psychedelic effects. Reportedly, MDMA's psychedelic effects are milder than those produced by hallucinogens such as LSD and mescaline. MDMA has been available as a street drug since the 1980s. Its use has escalated in the 1990s among college students and young adults, particularly those who participate in all-night dance parties called "raves." MDMA's street names include "ecstasy," "XTC," "clarity," "essence," and "Adam."

Methods of Use

MDMA is most often available in tablet form and is usually ingested orally. It is also available as a powder and is sometimes snorted and occasionally smoked but rarely injected.

Extent of Use

In 1998, 3.6 percent of 12th-graders, 3.3 percent of 10th-graders, and 1.8 percent of 8th-graders reported they had used MDMA in the past year, according to the NIDA-funded Monitoring the Future survey (MTF), which is conducted by the University of Michigan's Institute for Social Research.

MTF's followup of a group of graduates from each surveyed high school class indicates that the number of college students who had used MDMA during the past year rose from 0.9 percent in 1991 to 2.4 percent in 1997. Among young adults, annual MDMA use rose from 0.8 percent to 2.1 percent during the same period.

The NIDA-sponsored Community Epidemiology Work Group (CEWG), a network of researchers from 21 major U.S. metropolitan areas, also has reported increased MDMA use by young adults and adolescents in many areas of the country in recent years. At the December 1998 CEWG meeting, researchers from Atlanta, Boston, Chicago, Miami, New York City, and Washington, D.C., reported MDMA use at night clubs and raves by young adults and adolescents.

Effects of Use

MDMA stimulates the release of the neurotransmitter serotonin from brain neurons, producing a high that lasts from several minutes to an hour. The drug's rewarding effects vary with the individual taking it, the dose and purity, and the environment in which it is taken. MDMA can produce stimulant effects such as an enhanced sense of pleasure and self-confidence and increased energy. Its psychedelic effects include feelings of peacefulness, acceptance, and empathy. Users claim they experience feelings of closeness with others and a desire to touch them. Because MDMA engenders feelings of closeness and trust and has a short duration of action, some clinicians claim that the drug is potentially valuable as a psychotherapeutic agent. However, MDMA is classified by Federal regulators as a drug with no accepted medical use.

Health Hazards

MDMA users may encounter problems similar to those experienced by amphetamine and cocaine users, including addiction.

In addition to its rewarding effects, MDMA's psychological effects can include confusion, depression, sleep problems, anxiety, and paranoia during, and sometimes weeks after, taking the drug.

Physical effects can include muscle tension, involuntary teeth-clenching, nausea, blurred vision, faintness, and chills or sweating. Increases in heart rate and blood pressure are a special risk for people with circulatory or heart disease.

MDMA-related fatalities at raves have been reported. The stimulant effects of the drug, which enable the user to

dance for extended periods, combined with the hot, crowded conditions usually found at raves can lead to dehydration, hyperthermia, and heart or kidney failure.

MDMA use damages brain serotonin neurons. Serotonin is thought to play a role in regulating mood, memory, sleep, and appetite. Recent research indicates heavy MDMA use causes persistent memory problems in humans.

For More Information

Additional information about MDMA can be found on the NIDA home page on the World Wide Web at www.drugabuse.gov. Fact sheets and recorded messages about MDMA can also be found on Infofax, NIDA's automated information retrieval system, at (888) 644-6432. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 13, Number 6 (March, 1999)

Methamphetamine Abuse Alert

In response to indicators that show methamphetamine abuse increasing across the Nation, NIDA sent a bulletin containing current, science-based information on methamphetamine to more than 200,000 drug abuse treatment providers, hospital emergency room workers, and other health services practitioners.

The four-page Community Drug Alert Bulletin on Methamphetamine arms health care providers with important information they can use to mount effective prevention and treatment responses to methamphetamine's threat to the public health. Highlights are below.

What Methamphetamine Is

Methamphetamine is a powerfully addictive stimulant that dramatically affects many areas of the central nervous system. The drug has a high potential for widespread abuse because it can easily be made in clandestine laboratories from relatively inexpensive over-the-counter ingredients.

Methamphetamine can be purchased at a low cost, is available in many forms, and can be smoked, snorted, injected, or orally ingested.

Methamphetamine is sometimes called "speed," "meth," and "chalk." In its smoked form, the drug is often called "ice," "crystal," "crank," "fire," and "glass."

Who Uses Methamphetamine

Traditionally associated with white male blue-collar workers, methamphetamine reportedly is being used by diverse groups in all regions of the country.

Use is increasing among men who have sex with men and use other drugs; young adults who attend "raves" or go to private clubs; homeless and runaway youth; commercial sex workers; members of motorcycle gangs; and people in occupations that demand long hours, mental alertness, and physical endurance.

New Trends and Patterns of Use

Emerging evidence indicates that users increasingly are administering methamphetamine intravenously. Injecting the drug puts the user at increased risk of contracting HIV/AIDS, hepatitis, and other infectious diseases.

Often, methamphetamine is used in dangerous combination with other substances, including cocaine and "crack" cocaine, marijuana, heroin, and alcohol.

Methamphetamine is not usually sold and bought on the street. Users report that they obtain the drug from friends and acquaintances.

Methamphetamine, used primarily in urban areas of California, has become a substantial drug problem in other sections of the West and Southwest as well as rural and urban areas of the South and Midwest. Its use also is emerging in urban areas in the East.

Signs of Methamphetamine Use

Some common signs of methamphetamine use include:

- agitation, excited speech, decreased appetite, increased physical activity, dilated pupils, and nausea and vomiting;
- occasional episodes of sudden and violent behavior, intense paranoia, visual and auditory hallucinations, and bouts of insomnia; and
- a tendency to compulsively clean and groom and repetitively disassemble and sort objects.

Guidelines for Preventing Methamphetamine Use

Effective prevention of drug use begins with assessing the specific nature of the drug problem within the local community and adapting prevention programs accordingly. Prevention programs should start early, be comprehensive, and stress key points repeatedly. Family-focused prevention efforts have a greater impact than strategies that focus on parents only or children and adolescents only.

Guidelines for Treating Methamphetamine Addiction

Cognitive behavioral interventions that help modify a patient's thinking and harmful behaviors and teach skills to cope with stressful situations have been effective.

Currently no medications are available to treat methamphetamine addiction or overdose. However, antidepressant medications can be prescribed which can serve to combat the depressive symptoms frequently experienced during methamphetamine withdrawal.

For More Information

NIDA's Community Drug Alert Bulletin on Methamphetamine and the NIDA Research Report, Methamphetamine Abuse and Addiction (NCADI publication #PHD756) can be obtained from the National Clearinghouse for Alcohol and Drug Information, P.O. Box 2345, Rockville, MD 20847, 1-800-729-6686. These publications and additional information about methamphetamine can be found on the NIDA home page on the World Wide Web at www.nida.nih.gov. Fact sheets and recorded messages about methamphetamine abuse and addiction can also be found on Infofax, NIDA's automated information retrieval system, at (888) 644-6432.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 13, Number 6 (March, 1999)

Des Moines Town Meeting Addresses Methamphetamine Abuse Epidemic in Iowa

By Barbara Cire, *NIDA NOTES* Associate Editor

(Left to right) Iowa Governor Terry Branstad, NIDA Director Dr. Alan I. Leshner, and Iowa Senator Chuck Grassley at the Des Moines Town Meeting.

The latest in NIDA's Town Meeting series, held in Des Moines in October, focused on an epidemic of methamphetamine use under way in Iowa. The meeting was cosponsored by the Governor's Alliance on Substance Abuse, the Iowa Department of Public Health, and the Office of the Mayor of Des Moines. More than 300 policymakers, civic leaders, scientists, State officials, drug abuse prevention and treatment practitioners, health care providers, law enforcement personnel, and members of the general public attended the meeting.

"Methamphetamine abuse has reached epidemic proportions and is reaching into more sectors of society," said NIDA Director Dr. Alan I. Leshner. He told participants that NIDA had recently issued a Community Drug Alert Bulletin on methamphetamine abuse. (See "Tearoff") "We are here today to provide you with information about the results of NIDA-supported research on methamphetamine and other drugs and to suggest how you can use this information to address local problems. We want you to tell us what you need in terms of science-based information and materials."

According to Iowa law enforcement personnel, the State has seen a recent and dramatic increase in the use of methamphetamine. During 1998, a special law enforcement team raided and shut down more than 200 clandestine methamphetamine labs where the drug was being illegally manufactured. In 1997, the team raided and closed 63 labs.

Iowa Governor Terry E. Branstad had invited NIDA to hold the meeting in Des Moines to address the State's methamphetamine problem. "Today's meeting reminds us of the need to work together across disciplines to address critical issues such as the increasing use of methamphetamine and marijuana by younger Iowans," said Governor Branstad. "The knowledge gained here will serve to enhance the good work already being performed in the areas of substance abuse prevention, treatment, and law enforcement in Iowa communities."

(Left to right) NIDA Director Dr. Alan I. Leshner, a Town Meeting participant, and Dale Woolery of the Iowa Governor's Alliance on Substance Abuse view a mock-up of a home-based methamphetamine lab.

NIDA Associate Director Dr. Timothy P. Condon presented an overview of research on methamphetamine abuse, prevention, and addiction treatment. He also

discussed the changing epidemiology of methamphetamine use. "In the past, typical methamphetamine users were white, male, high school graduates 20 to 35 years old and of low to moderate income," he said. "But, an increasing number of women and people older than 35 are beginning to use methamphetamine."

The day-long meeting featured discussions on how drugs work in the brain, advances in drug abuse prevention and addiction treatment, and how managed care affects drug abuse treatment services. Participants queried presenters about potential new treatments for methamphetamine addiction, ways of communicating with young people about the dangers of methamphetamine and other drugs, and how drugs cause changes in the brain. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

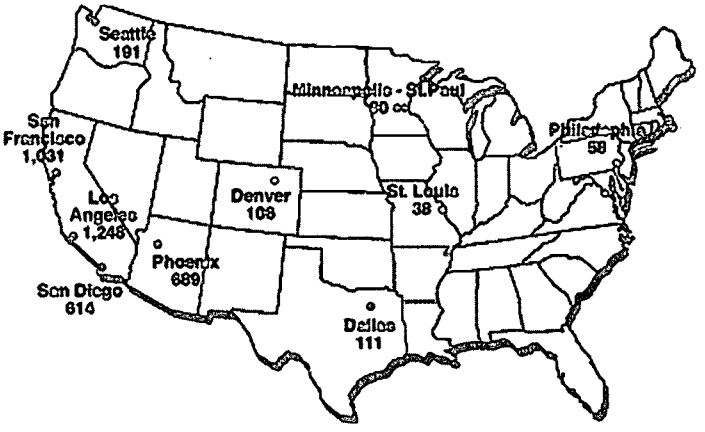
Research Findings

Volume 13, Number 1 (June, 1998)

NIDA Initiative Tackles Methamphetamine Use

By Robert Mathias, *NIDA NOTES* Staff Writer

In response to an upsurge in heroin use among America's young people in recent years, NIDA convened a national research-based conference on Heroin Use and Addiction in Washington, D.C., this past September. The well-attended conference drew more than 600 participants who examined all aspects of the changing nature of heroin use in the United States and shared scientific information and approaches to preventing and treating heroin abuse and addiction. Representatives of national drug abuse organizations, scientists, prevention and treatment practitioners, and criminal justice personnel took part in the conference.



The numbers on the map represent the number of patients in these metropolitan areas who sought hospital emergency department treatment due to methamphetamine use.

Source: Year-End Preliminary Estimates from the 1996 Drug Abuse Warning Network, Substance Abuse and Mental Health Services Administration.

NIDA has launched an Institute-wide initiative to expand scientific research on methamphetamine and apply the findings to the prevention and treatment of methamphetamine abuse. The Methamphetamine Initiative is aimed at increasing scientific knowledge about methamphetamine and providing the public and health care practitioners with the latest available information about the drug's use, consequences, prevention, and treatment.

Methamphetamine, also called "meth," is a potent, highly addictive form of amphetamine. Use of the drug has been a major problem in western areas of the United States since the mid- to late 1980s and has been increasing in other areas of the country, such as the South and Midwest, since the early 1990s, according to reports from NIDA's Community Epidemiology Work Group (CEWG). Traditionally, methamphetamine use has been centered among white working class males and men who have sex with men. However, recent CEWG reports and drug use surveys indicate that use of the drug also may be increasing among other groups such as Hispanics in Los Angeles and adolescents in rural areas.

"We know from research that methamphetamine is a powerfully addictive stimulant associated with serious health conditions including brain damage, memory loss, psychotic-like behavior, heart damage, hepatitis, and HIV transmission," NIDA Director Dr. Alan I. Leshner said in discussing the Initiative's opening thrust—a NIDA-sponsored western regional methamphetamine symposium held in San Francisco in December 1996.

At that meeting, scientists, civic leaders, policymakers, public officials, and drug abuse prevention and treatment professionals discussed ways to improve State and local prevention and treatment responses to methamphetamine abuse.

Last year, NIDA received $4.2 million in supplemental funding from the White House Office of National Drug Control Policy to expand the Institute's program of methamphetamine research. This year, the Director's Office of the National Institutes of Health awarded an additional $2 million in special funds to NIDA for methamphetamine research. NIDA is using these monies to broaden the Initiative's methamphetamine research in the following areas: basic and clinical neurobiology, long-term effects of abuse, epidemiology and prevention, drug abuse treatment and health services, and medications development.

The Initiative's basic and clinical neurobiology research is aimed at better understanding the mechanisms that underlie methamphetamine's addictive potential and the adverse consequences of its chronic abuse. Previous research has shown that methamphetamine, like cocaine, achieves its euphoric effect by increasing the extracellular concentration of the neurotransmitter dopamine in the brain. However, methamphetamine and cocaine achieve their dopamine-enhancing effects through different cellular mechanisms. In addition, methamphetamine remains

in the brain much longer than cocaine does and damages brain cells of animals that have been chronically exposed to the drug. (See "Comparing Methamphetamine and Cocaine")

Researchers supported by NIDA's Division of Basic Research (DBR) under the Initiative, such as Dr. Paul Vezina at the University of Chicago, now are trying to unravel the underlying mechanisms through which animals chronically exposed to methamphetamine become more sensitive, or respond more strongly, to the drug. "The hypothesis in the field is that sensitization is linked to addiction," explains DBR's Dr. Jerry Frankenheim. Therefore, another basic research study, by Dr. Stephen Strakowski of the University of Cincinnati College of Medicine, is studying the process of stimulant sensitization in humans using amphetamine, which is closely related chemically to methamphetamine. The study is examining whether there is a link between stimulant sensitization in humans and their liking the drug and craving it later on. In other research, Dr. William Melega at the University of California at Los Angeles is examining how methamphetamine-induced neurotoxicity affects the behavior of animals.

"This basic research is key to understanding the differences between cocaine and methamphetamine," says Dr. Frankenheim. "The results of this research will help us determine if we need somewhat different approaches to preventing and treating methamphetamine and cocaine abuse," he says.

The Initiative also is trying to determine whether the methamphetamine-induced neurotoxicity that studies have shown in animals also occurs in humans. For example, Dr. George A. Ricaurte of The Johns Hopkins Medical Institutions in Baltimore is conducting brain imaging studies with long-term methamphetamine users to assess how chronic methamphetamine use affects the human brain, cognition, and other physiological functions. In addition, postmortem studies of the brains of chronic methamphetamine abusers are being conducted by Dr. Stephen Kish of the Clarke Institute of Psychiatry in Toronto, Canada. The studies will provide additional information about the long-term effects of methamphetamine abuse on human brain structure. In living humans, these effects on brain structure could affect brain function.

The Methamphetamine Initiative also is expanding NIDA's research on preventing methamphetamine abuse and addiction. For example, Dr. Steve Sussman of the University of Southern California has been developing a promising drug abuse prevention intervention for students in continuation or alternative public high schools in southern California. More than 10 percent of students participating in Dr. Sussman's ongoing prevention study are known to have used methamphetamine in the past. Now, Dr. Sussman is expanding his research to examine current methamphetamine use among these youths and to assess whether the two experimental drug abuse prevention programs he has been developing can prevent methamphetamine use in this population. (For more information on Dr. Sussman's research, see "Specialized High School Prevention Programs Target At-Risk Adolescents," *NIDA NOTES*, May/June 1997)

The Initiative also is aiming to resolve puzzling patterns of methamphetamine abuse in the United States. "Why has methamphetamine use occurred predominantly in the western United States and Hawaii?" asks Dr. Zili Sloboda, who directs NIDA's Division of Epidemiology and Prevention Research (DEPR). To answer this and other questions about shifting patterns of methamphetamine use, DEPR is launching a study in five cities where methamphetamine use is high or where a methamphetamine problem may be emerging. This study will identify characteristics of methamphetamine users, patterns of initiation and use, and consequences of use, says Dr. Sloboda. Ultimately, the findings of this research will be used to develop more effective methamphetamine prevention programs, she says.

Development of behavioral treatments tailored to the specific needs of methamphetamine-abusing populations also is being emphasized under the Initiative. For example, men who have sex with men represent a significant target group for methamphetamine treatment interventions. Previous research shows that methamphetamine use is high in this population and is linked to high-risk sexual behaviors and the transmission of HIV. NIDA's Division of Clinical and Services Research (DCSR) has funded a new behavioral treatment research study among gay and bisexual male methamphetamine users in Los Angeles. This study, which is being conducted by Dr. Steven Shoptaw of the Los Angeles Treatment Research Center, will compare the relative effectiveness of contingency management, relapse prevention, and enhanced HIV counseling methods in reducing methamphetamine use and related high-HIV-risk sexual behaviors. DCSR also is expanding several studies that have been testing other promising behavioral treatments with cocaine-abusing populations. The goal is to see whether these treatments are appropriate and can be adapted to treat methamphetamine abuse and associated behaviors effectively, says the Division's Dr. Dorynne Czechowicz.

The development of medications to reduce methamphetamine abuse and craving and to repair brain systems damaged by chronic methamphetamine use is another major Initiative priority. In seeking potential treatment compounds to reduce methamphetamine abuse, NIDA's Medications Development Division (MDD) is capitalizing on the substantial research that has been done to develop cocaine treatment medications. Though the initial

mechanisms of action for cocaine and methamphetamine differ, ultimately they both greatly increase the levels of dopamine between brain cells, points out Dr. Betty Tai of MDD. "From that point, the cascade of events from the cellular all the way to behavioral is quite similar," she says. Therefore, any compound that has shown promise for treating cocaine abuse by producing a milder dopamine effect could be tested as a potential methamphetamine treatment medication, Dr. Tai says. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 13, Number 1 (June, 1998)

NIDA Expands Research to Meet Challenge of Methamphetamine Abuse

NIDA Director Dr. Alan I. Leshner

Since the late 1980s, use of methamphetamine, a powerful central nervous system stimulant, has been a problem in western areas of the United States. More recently, NIDA's drug abuse monitoring systems and surveys show that use of the drug has been increasing in these areas and spreading to other areas of the country.

To counter this serious threat to the public health, NIDA has launched a comprehensive Methamphetamine Initiative that is stimulating research to fill gaps in the scientific knowledge about the pharmacology, toxicity, epidemiology, prevention, and treatment of methamphetamine abuse. At the same time, the Initiative is providing the public and health care practitioners with the latest available research information about methamphetamine to enable them to take action against methamphetamine use.

The Initiative will provide the additional scientific knowledge we need to develop more effective prevention and treatment approaches that can help communities respond to this complex public health problem.

The Methamphetamine Initiative builds on and complements the substantial body of knowledge yielded by previous NIDA-supported methamphetamine research. That research shows that smoking, snorting, ingesting orally, or injecting methamphetamine produces a long-lasting euphoria by stimulating excessive levels of the neurotransmitter dopamine in areas of the brain related to pleasure. Use of this powerful stimulant is associated with serious health consequences including addiction, memory loss, and potential heart and brain damage. Other damaging effects of use include aggression and violent and psychotic behavior. In addition, methamphetamine use is associated with increased transmission of hepatitis and HIV/AIDS.

We launched our Methamphetamine Initiative in San Francisco with a regional symposium on methamphetamine abuse, prevention, and treatment issues in December 1996. This symposium was an important step toward one of NIDA's most important goals for the Initiative—to translate the knowledge developed through research into a better public understanding of methamphetamine abuse and the implementation of more effective methamphetamine prevention and treatment strategies in the community.

Last year, NIDA received $4.2 million from the White House Office of National Drug Control Policy to broaden our ongoing program of methamphetamine research. This year, the Director's Office of the National Institutes of Health awarded NIDA an additional $2 million in special funds for additional methamphetamine research. The funds were devoted particularly to the development of new medications for methamphetamine overdose and addiction. (For full details of the Initiative, see "NIDA Initiative Tackles Methamphetamine Use")

Our Initiative includes basic animal and human neuroimaging studies that will increase our understanding of the neurobiological mechanisms and consequences of methamphetamine use. Previous research has shown that prolonged exposure to relatively low levels of methamphetamine can damage as much as 50 percent of the dopamine-producing nerve cells in the brains of animals. NIDA-funded scientists now are studying whether, as we suspect, similar damage occurs in the brains of humans. These researchers also are looking at how such brain damage might affect the physiological functions and behavior of chronic methamphetamine abusers. One of the important questions this research will try to answer is whether such brain damage is linked to the hallucinations, paranoia, and violent behavior that sometimes accompany chronic methamphetamine use.

NIDA also is expanding its epidemiology research to help us answer questions about who is using methamphetamine and what promotes or inhibits the use of the drug. We need to know why methamphetamine use has been an ongoing problem in the western United States and Hawaii but not in eastern cities. We need to identify factors that

underlie the apparent recent spread of methamphetamine use to other areas of the country, including rural and urban areas of the South and Midwest. We also need to understand why methamphetamine use traditionally has been associated with white, male blue-collar workers and to determine what factors are now spurring its use by more diverse groups.

To answer such questions, NIDA recently launched a multisite study in cities where methamphetamine use is high and cities where use is low. The results of this research will provide the scientific base for developing more effective targeted methamphetamine prevention approaches. This will help forestall the spread of methamphetamine use and its harmful consequences to new groups and areas of the country.

We know that methamphetamine injection increases risk for contracting and transmitting HIV because injection drug use is a risk factor in nearly one-third of Americans infected with HIV. Furthermore, use of methamphetamine is associated with an increase in high-risk sexual behaviors that can contribute to the spread of HIV/AIDS. These behaviors represent a significant public health problem among gay and bisexual methamphetamine abusers in cities such as Los Angeles, San Francisco, and Seattle. Therefore, our Initiative is supporting a number of new and expanded studies to develop methamphetamine treatment interventions that target these populations. Using information gleaned from past treatment research, these studies are testing behavioral interventions, such as contingency management and relapse prevention. These approaches are designed to help modify methamphetamine abusers' thinking and behaviors, to increase their coping skills, and to reduce both methamphetamine abuse and associated HIV-risk behaviors.

In conjunction with our behavioral therapies development, the Initiative also is working to develop medications to reduce methamphetamine use. This effort is capitalizing on knowledge provided by our previous neurobiological research. We also are supporting research to develop medications that would ameliorate the harmful consequences of chronic methamphetamine abuse. For example, antidepressant medications are helpful in combating the depressive symptoms often seen in methamphetamine users who have recently stopped using the drug.

We know that methamphetamine injection increases risk for contracting and transmitting HIV.

To help disseminate useful scientific information about methamphetamine abuse and its consequences that our research has given us, NIDA has developed a new research report on methamphetamine abuse and addiction. The report will provide the general public, policymakers, health care practitioners, and prevention and treatment service providers with an overview of the latest research findings on methamphetamine.

Recently, I was appointed to serve on a Methamphetamine Interagency Task Force, chaired by Attorney General Janet Reno and Office of National Drug Control Policy Director General Barry McCaffrey, that is working to enhance the Federal Government's education, prevention, and treatment practices and strategies to address methamphetamine abuse. The broad range of new research activities now being conducted under NIDA's Methamphetamine Initiative will provide the additional scientific knowledge we need to develop more effective prevention and treatment approaches that can be disseminated to help communities respond more effectively to all aspects of this complex public health problem.

For More Information

The NIDA research report, Methamphetamine Abuse and Addiction (NCADI publication #PHD756), can be obtained from the National Clearinghouse for Alcohol and Drug Information, P.O. Box 2345, Rockville, MD 20847, 1-800-729-6686.

This publication and additional information about methamphetamine abuse and addiction also can be found on the NIDA World Wide Web site at http://www.nida.nih.gov. Fact sheets and recorded messages about methamphetamine abuse and addiction also can be found on NIDA's new Infofax line: 1-888-644-6432. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 13, Number 1 (June, 1998)

Comparing Methamphetamine and Cocaine

Methamphetamine and cocaine belong to the broad class of drugs called psychostimulants that also includes amphetamine and methylphenidate. The two drugs often are compared to each other because they produce similar mood-altering effects and both have a high potential for abuse and dependence. Methamphetamine and cocaine also share other similarities. However, the two drugs also exhibit significant differences. Here are some of these similarities and differences.

Sources

- Methamphetamine is man-made.
- Cocaine is plant-derived.

Common Methods of Use

- Both methamphetamine and cocaine are commonly smoked, injected intravenously, or snorted.
- Methamphetamine also is commonly ingested orally.

Geographic Patterns of Use

- Methamphetamine use is highest in Honolulu, Hawaii, and western areas of the continental United States, particularly urban areas of California, Washington, Oregon, Colorado, and Arizona. In recent years, methamphetamine use has increased in both rural and urban areas of the South and Midwest. (Source: Epidemiologic Trends in Drug Abuse: Advance Report, 1997, NIDA.)
- Cocaine use shows no clear geographic pattern; regional rates of use vary from year to year. Cocaine use also is significantly higher in large metropolitan areas than in nonmetropolitan areas. (Source: Preliminary Results from the 1996 National Household Survey on Drug Abuse, Substance Abuse and Mental Health Services Administration.)

Euphoric Effects

- When they are smoked or injected intravenously, both methamphetamine and cocaine produce an intense, extremely pleasurable "rush" almost immediately, followed by euphoria, referred to as a "high."
- When snorted, both methamphetamine and cocaine produce no intense rush and take longer to produce a high; orally ingested methamphetamine produces a similar effect.
- Methamphetamine's high lasts anywhere from 8 to 24 hours, and 50 percent of the drug is removed from the body in 12 hours.
- Cocaine's high lasts anywhere from 20 to 30 minutes, and 50 percent of the drug is removed from the body in 1 hour.

Physical and Mental Effects

- The immediate effects of both methamphetamine and cocaine can include irritability and anxiety; increased body temperature, heart rate, and blood pressure; and possible death.
- Methamphetamine's and cocaine's short-term effects also can include increased activity, respiration, and wakefulness, and decreased appetite.
- Effects of chronic abuse of either methamphetamine or cocaine can include dependence and possible stroke.
- Chronic abuse of either methamphetamine or cocaine also can lead to psychotic behavior characterized by paranoia, hallucinations, mood disturbances, and violence. Anecdotal evidence suggests that violent behavior may be more common among chronic methamphetamine users than it is among chronic cocaine users.
- Drug craving, paranoia, and depression can occur in addicted individuals who try to stop using either methamphetamine or cocaine.

Neurotoxic Effects

- Methamphetamine is neurotoxic in animal species ranging from mice to monkeys; the drug damages the neurons that produce the neurotransmitters dopamine and serotonin. The usual doses taken by human methamphetamine abusers are comparable to the doses that produce neurotoxicity in animals.
- Cocaine is not neurotoxic to dopamine and serotonin neurons.

Transmission of HIV/AIDS

- Both methamphetamine and cocaine use contributes to transmission of HIV/AIDS through intravenous injection.
- Methamphetamine use in conjunction with high-risk sexual behaviors and cocaine use in "sex-for-crack" exchanges also contribute to transmission of HIV/AIDS. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

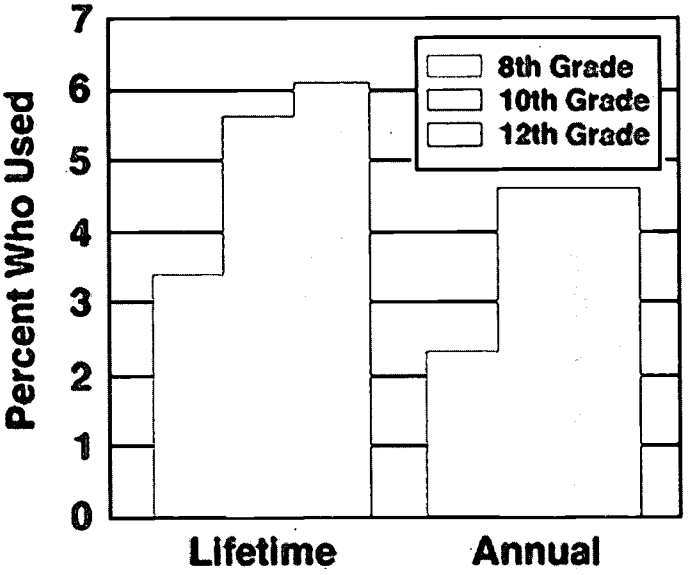
Volume 12, Number 2 (March/April 1997)

Study Takes a Closer Look at "Ecstasy" Use

The synthetic drug "ecstasy," which has been used increasingly among college students and young adults in recent years, also is being used at relatively high levels by America's 8th, 10th, and 12th graders, according to NIDA's 1996 Monitoring the Future study. Nearly 5 percent of 10th and 12th graders and about 2 percent of 8th graders said they had used MDMA in the past year, the study reported.

Ecstasy, or MDMA (3,4-methylenedioxymethamphetamine), is structurally similar to methamphetamine and the hallucinogen mescaline. Previous Monitoring the Future studies asked 12th graders about the use of MDMA by their friends and about the drug's availability. The 1996 study was the first to question 8th, 10th, and 12th graders about their own use of the drug. The new data on MDMA use among these students will provide baseline information that will be helpful in tracking trends in MDMA use from a younger age.

MDMA use has risen sharply among college students and young adults during the 1990s, according to the 1995 Monitoring the Future study. The 1995 study included followup data on drug use among a representative sample of college students and young adults who had previously taken part in the study when they were in high school. College students and young adults in this sample have been surveyed every 2 years since the Monitoring the Future study began in 1976. (For more information about MDMA, see "Like Methamphetamine, 'Ecstasy' May Cause Brain Damage," *NIDA NOTES*, November/December 1996) NN



The 1996 Monitoring the Future study is the first to provide data on 8th, 10th, and 12th graders' use of Ecstasy.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 11, Number 5 (November/December 1996)

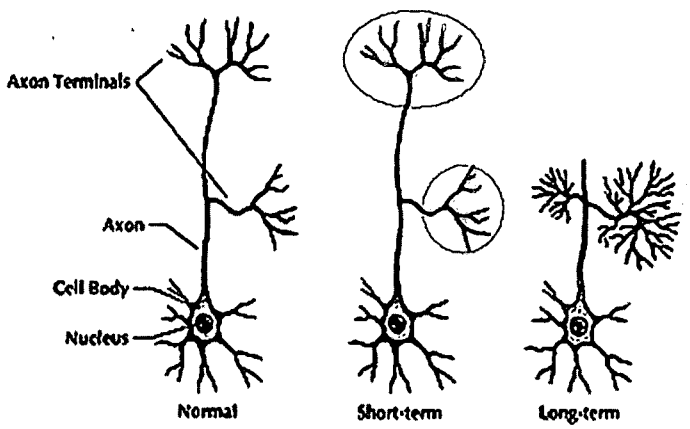
Like Methamphetamine, "Ecstasy" May Cause Long-Term Brain Damage

By Robert Mathias, *NIDA NOTES* Staff Writer

Heavy users of ecstasy, a synthetic drug that is structurally similar to methamphetamine and the hallucinogen mescaline, may be risking brain damage that remains long after the high has worn off, according to NIDA-supported research.

In a series of studies conducted with rats and nonhuman primates, Dr. George Ricaurte and his colleagues at Johns Hopkins Medical Institutions first determined that a single dose of MDMA (3,4-methylenedioxymethamphetamine), only slightly higher than the size of doses taken by humans, significantly damaged brain cells called neurons that produce serotonin. Serotonin is a major neurotransmitter, or chemical messenger, in the brain that is thought to influence mood, appetite, sleep, and other important functions. Then Dr. Ricaurte reported that 12 to 18 months after the brains of squirrel monkeys had been damaged by MDMA, serotonin-producing nerve fibers had regrown abnormally in some brain regions and failed to regrow at all in others.

Unlike methamphetamine, which damages brain neurons that produce both serotonin and another important chemical messenger called dopamine, "MDMA selectively damages serotonin neurons in virtually all species examined to date," Dr. Ricaurte says.



Dr. Ricaurte's studies have found that MDMA damages serotonin-producing neurons in the brains of nonhuman primates. The illustration on the left shows a normal neuron. The shaded area in the middle illustration shows the axon terminals of the neuron that are damaged by MDMA. The illustration on the right shows how, 12 to 18 months after being damaged by MDMA, serotonin-producing nerve fibers have regrown excessively in some areas and not at all in others.

"With MDMA, the doses that people take very closely approach the doses known to produce neurotoxic effects in animals," Dr. Ricaurte says.

"At this point, the major question is whether the neuronal changes we see in animals from methamphetamine and MDMA exposure occur in human beings who use these drugs," he says.

To help answer that question, he is conducting separate clinical studies using brain imaging techniques to evaluate the possibility of long-term brain damage in humans who have previously used either methamphetamine or MDMA. These studies also are assessing the potential functional consequences of such neuronal damage on aspects of mood, movement, memory, impulse control, aggression, and sleep cycles.

Determining the functional consequences of MDMA exposure may be more complex than previously thought, Dr. Ricaurte says. The long-term study with squirrel monkeys indicated that in some brain areas, such as those containing structures involved in memory and learning, damaged neurons failed to recover. However, in other brain areas, specifically those involved in regulating such functions as sleep and appetite, damaged neurons regrew nerve fiber excessively, resulting in an overabundance of serotonin being released. "This means that when we evaluate humans previously exposed to high doses of MDMA, we should be looking for loss of serotonin function in some brain regions, but perhaps normal or increased serotonin function in other regions," Dr. Ricaurte says.

Determining the possible damaging effects of ecstasy has become more important in recent years because the pattern of MDMA use has changed, points out Dr. Ricaurte. Although ecstasy has been available as a street drug since the 1980s, its use escalated in the 1990s among college students and young adults, particularly those who participate in all-night dance parties called "raves." In 1995, 2.3 percent of college students said they had used ecstasy at some time during the year, more than quadruple the 0.5 percent of students who reported using the drug in 1994,

according to NIDA's latest Monitoring the Future study. The percentage of young adults, ages 19 to 28, who used ecstasy in the past year also jumped significantly to 1.6 percent in 1995 from 0.7 percent in 1994, according to the survey.

Source:

- Fischer, C.; Hatzidimitriou, G.; Wlos, J.; Katz, J.; and Ricaurte, G. Reorganization of ascending 5-HT axon projections in animals previously exposed to recreational drug 3,4-methelenedioxymetham-phetamine (MDMA, "Ecstasy"). *Journal of Neuroscience* 15:5476-5485, 1995. NN

63

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 11, Number 5 (November/December 1996)

Response to Escalating Methamphetamine Abuse Builds on NIDA-Funded Research

By Neil Swan, *NIDA NOTES* Staff Writer

NIDA-funded scientists are providing research crucial to the Nation's response to increasing methamphetamine abuse and addiction. Methamphetamine, also called "meth," is a potent form of amphetamine. It is a synthetic, highly addictive stimulant that is cheaper and longer lasting than cocaine.

Methamphetamine comes in many forms and can be smoked, snorted, orally ingested, or injected. The drug is a white, odorless, bitter-tasting crystalline powder that can be dissolved in water or alcohol. When made in clandestine labs, it is often in the form of a coarse powder or chunks that are off-white to yellow. Other nicknames include "speed," "crank," and "zip." The smokable form of the drug may be called "ice" or "crystal." The drug is addictive, and users can escalate quickly to larger and more frequent doses. Chronic abuse can lead to violent behavior. (For more information, see Facts About Methamphetamine)

The growing abuse of the drug is linked to its increasing availability and the fact that it can be easily manufactured from readily available chemical ingredients. Congress last summer passed the Comprehensive Methamphetamine Control Act establishing new controls over volume sales of the chemical ingredients used to produce the drug.

NIDA's Community Epidemiology Work Group (CEWG), a network of epidemiologists and researchers from 20 major U.S. metropolitan areas that provides frontline surveillance of the nature and extent of drug abuse, confirms that methamphetamine use has been prevalent in west coast cities and in western and southwestern communities, including many rural areas. Abuse of the drug now is being reported in urban settings in widening areas of the West, Midwest, and elsewhere. Methamphetamine is the dominant illicit drug problem in San Diego, according to CEWG data that include records of hospital emergency room admissions, drug-related deaths, and police drug seizures; and local observations of street buys and drug-trafficking patterns. Honolulu and San Francisco also have substantial methamphetamine-using populations, according to CEWG data. Recent reports indicate increasing patterns of methamphetamine use in Denver, Los Angeles, Minneapolis, Phoenix, Seattle, and Tucson as well.

Until recently, the drug's manufacture generally was dispersed so that small quantities were produced in rural areas. There are indications that methamphetamine now is being manufactured on a larger scale by organized groups operating out of Mexico and southern California. Methamphetamine of Mexican origin is now found along newly extended trafficking routes in several States, including Arizona, Colorado, Iowa, Missouri, Nebraska, and Texas, according to CEWG. Clandestine labs have produced the drug in rural and desert areas where the telltale odors of the production process are less likely to be detected. Mobile labs in campers and vans have been reported in Washington.

A NIDA-funded study in Seattle confirmed that methamphetamine use was widespread among the city's homosexual and bisexual populations. Members of these groups using methamphetamine reported they practice sexual and needle-use behaviors that place them at heightened risk of contracting and transmitting HIV, the virus that causes AIDS. NIDA also supports basic research examining the neurobiological mechanisms involved in methamphetamine's action in the brain, seeking knowledge necessary for long-term solutions to abuse of the drug. Research has shown that methamphetamine releases high levels of the neurotransmitter dopamine, which stimulates brain cells, causing enhanced mood and increased body movement.

Animal studies show that high doses of methamphetamine damage nerve cells. In rats, one high dose of methamphetamine is enough to cause damage. Prolonged dosage seems to make it worse.

Another major research focus is on methamphetamine's neurotoxicity, specifically its action in damaging brain cells that contain dopamine and serotonin, another neurotransmitter. Scientists think that methamphetamine abuse over time may cause reduced levels of dopamine, which

can cause symptoms like those of Parkinson's disease, a severe movement disorder.

Animal studies going back more than 20 years show that high doses of methamphetamine damage neuron cell-endings, says Dr. Lewis S. Seiden of the University of Chicago, a NIDA-funded researcher who has studied methamphetamine for many years. "The damage is essentially permanent, although there may be some regrowth. The damage occurs in rats, guinea pigs, pigs, cats, and nonhuman primates. In rats, one high dose of methamphetamine is enough to cause damage. Prolonged dosage seems to make it worse," he says. Recent NIDA-funded studies by Dr. George A. Ricaurte at Johns Hopkins Medical Institutions in Baltimore and by other scientists indicate that neurotoxic effects are more pronounced in nonhuman primates than in rodents.

Dopamine- and serotonin-containing neurons do not die after methamphetamine use, but their nerve endings or terminals are cut back or "pruned" by use of the drug, Dr. Ricaurte says. "The question is, does the same thing occur in humans?" he asks. "To answer that question we have recently developed brain imaging techniques to study these effects in humans who have previously used methamphetamine." (See NIDA-Supported Researchers Use Brain Imaging to Deepen Understanding of Addiction)

Another NIDA-funded researcher, Dr. Glen R. Hanson at the University of Utah, found evidence that dopamine-generated compounds called free radicals that appear following methamphetamine use can affect serotonin production in contrasting ways. He also reports that several neuropeptide systems linked to dopamine brain pathways are profoundly altered by administration of low to high doses of methamphetamine.

"Our results suggest that high and low doses of methamphetamine affect a peptide called neurotensin in very different ways," says Dr. Hanson. High doses of methamphetamine limit neurotensin's function, perhaps resulting in exaggerated dopamine responses to the stimulant. Low doses of methamphetamine increase neurotensin levels and function, which in turn appear to counteract behavioral response to the drug. These findings suggest that neurotensin perhaps could be used to prevent excessive and damaging dopamine responses to methamphetamine, he adds.

NIDA is also supporting research into treatment for methamphetamine abuse. Dr. Richard A. Rawson of the Matrix Institute in Beverly Hills, California, is conducting two outpatient studies with patients using both cocaine and methamphetamine.

One study concerns a small group of gay, methamphetamine-using males in Hollywood, California, where use of the drug is closely related to high-risk sexual behavior. Methamphetamine is the "drug of choice" among these homosexual men whether it is snorted, injected, or smoked, says Dr. Rawson. "They all talk about the interconnectedness of their sexual behavior and methamphetamine use."

Another study concerns 600 heterosexual methamphetamine abusers seeking treatment at a facility in a rural area of San Bernardino County, California. Methamphetamine abuse has been a problem in this area since the late 1980s. Users typically have also used cocaine but find methamphetamine longer lasting and more easily available; many of those in treatment say they can readily get the drug, even at their work sites or public places like truck stops, says Dr. Rawson.

"Treatment response was somewhat poorer among methamphetamine abusers than among cocaine abusers—fewer meth abusers could remain drug free," he says. "The methamphetamine abusers are twice as likely as cocaine abusers to require some kind of medical treatment," he says. "Methamphetamine abusers are more debilitated and show paranoia and hallucinations. There is more violence associated with methamphetamine abuse, according to the treatment staff."

Concern that methamphetamine abuse is a growing problem affecting many population groups has prompted the White House to launch a policy and planning approach called the President's National Strategy for Combating Methamphetamine Abuse. The White House Office of National Drug Control Policy sponsored a Western Regional Methamphetamine Conference last January in San Francisco and will sponsor a national methamphetamine conference in May in Omaha, Nebraska.

The Substance Abuse and Mental Health Services Administration, in collaboration with NIDA, in June sponsored a satellite meeting on methamphetamine abuse at the annual meeting of the College on Problems of Drug Dependence in Puerto Rico. This meeting involved more than 30 experts, many of them NIDA staffers and NIDA-funded researchers. (See Recommendations to Advance Understanding of Methamphetamine, for a report on the meeting's recommendations.)

NIDA also sponsored a symposium, "Methamphetamine Abuse, Treatment, and Prevention," in San Francisco in December 1996 focusing on national and regional issues relating to methamphetamine abuse.

Sources

- Community Epidemiologic Work Group, Epidemiologic Trends in Drug Abuse, National Institute on Drug Abuse, Vol. 1. NIH, Publication No. 96-4126; Vol. 2, NIH Publication No. 96-4127, June 1996.

- Richards, J.B.; Baggot, M.J.; Sabol, K.E.; and Seiden, L.S. A high-dose methamphetamine regimen results in long-lasting deficits on performance of a reaction-time task. *Brain Research* 627:254-260, 1993.
- Wagstaff, J.D.; Gibb, J.W.; and Hanson, G.R. Microdialysis assessment of methamphetamine-induced changes in extracellular neurotensin in the striatum and nucleus accumbens. *Journal of Pharmacology and Experimental Therapeutics* 278(2):1-8, 1996.
- McCann, U., and Ricaurte, G. Strategies for detecting subclinical monoamine depletion in humans. In: L. Erinoff, ed., Assessing Neurotoxicity of Drugs of Abuse. NIDA Research Monograph 136, NIH Publication No. 93-3644, Washington, DC: GPO, 1993. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 11, Number 5 (November/December 1996)

Facts About Methamphetamine

Methamphetamine is a central nervous system stimulant with a high potential abuse and dependence. A synthetic drug, methamphetamine is closely related chemically to amphetamine, but produces greater effects on the central nervous system. The drug's euphoric effects are similar to but longer lasting than those of cocaine.

Methamphetamine takes the form of a white, odorless, and bitter-tasting crystalline powder, readily soluble in water or alcohol. Street methamphetamine is referred to by many names including "meth," "speed," "zip," "go-fast," "cristy," "chalk," and "crank." Pure methamphetamine hydrochloride, the smokable form of the drug, is called "L.A." or—because of its clear, chunky crystals—"ice" "crystal," "glass," or "quartz."

Methods and Effects of Use

Methamphetamine can be smoked, injected intravenously, snorted, or ingested orally. The drug alters mood in different ways, depending on how it is taken. Immediately after smoking or intravenous injection, the user experiences an intense "rush" or "flash" that lasts only a few minutes and is described as extremely pleasurable. Smoking or injecting produces effects fastest, within 5 to 10 seconds. Snorting or ingesting orally produces euphoria—a high but not an intense rush. Snorting produces effects within 3 to 5 minutes, and ingesting orally produces effects within 15 to 20 minutes.

Even small amounts of methamphetamine can produce euphoria, enhanced wakefulness, increased physical activity, decreased appetite, and increased respiration. Other central nervous system effects include athetosis (writhing, jerky, or flailing movements), irritability, insomnia, confusion, tremors, anxiety, aggression, hyperthermia, and convulsions. Hyperthermia and convulsions sometimes can result in death.

Cardiovascular side effects include chest pain and hypertension and sometimes can result in cardiovascular collapse and death. In addition, methamphetamine causes increased heart rate and blood pressure and sometimes can cause irreversible damage to blood vessels in the brain, producing strokes. Methamphetamine abuse during pregnancy may result in prenatal complications, increased rates of premature delivery, and altered neonatal behavioral patterns.

Psychological symptoms of prolonged methamphetamine abuse can resemble those of schizophrenia and are characterized by paranoia, hallucinations, repetitive behavior patterns, and formication (delusions of parasites or insects on the skin). Methamphetamine-induced paranoia can result in homicidal or suicidal thoughts. Although no characteristic physical signs of withdrawal are associated with methamphetamine abuse, users report drug craving, depressed mood, sleepiness, and hunger.

Extent of Use

NIDA's 1996 Monitoring the Future study, which assessed the extent of drug use among 8th-, 10th-, and 12th-graders across the country, reports that:

- When high school seniors were asked if they had used crystal methamphetamine at least once in their lifetimes, 4.4 percent said they had—an increase from 2.7 percent in 1990;
- In that same year, when high school seniors were asked if they had used crystal methamphetamine in the 12 months prior to the survey, 2.8 percent said they had-an increase from 1.3 percent in 1990.

The Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network reports that from 1991 to 1994, the number of methamphetamine-related visits to hospital emergency departments more than tripled, from 4,887 to 17,397.

More Information

For more information about methamphetamine, contact the National Clearinghouse for Alcohol and Drug Information (NCADI), P.O. Box 2345, Rockville, MD 20847, at 1-800-729-6686. Information is also available at the NCADI Web site at http://www.health.org or at the NIDA Web site at http://www.nida.nih.gov/ NN

67

NIDA

NATIONAL INSTITUTE

ON DRUG ABUSE

Printed July 2003

U.S. Department of Education
Office of Educational Research and Improvement (OERI)
National Library of Education (NLE)
Educational Resources Information Center (ERIC)

NOTICE

Reproduction Basis

☐ This document is covered by a signed "Reproduction Release (Blanket)" form (on file within the ERIC system), encompassing all or classes of documents from its source organization and, therefore, does not require a "Specific Document" Release form.

☒ This document is Federally-funded, or carries its own permission to reproduce, or is otherwise in the public domain and, therefore, may be reproduced by ERIC without a signed Reproduction Release form (either "Specific Document" or "Blanket").